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ORIGINAL ARTICLES

EFFECTS OF LARGE LOADS OF ELECTROLYTES

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OPTIMAL retention of an electrolyte by a growing infant will depend on a correct adjustment of outgo to intake. In the event of an abrupt increase of intake, this adjustment will require a time interval over which retention will rise beyond the requirement for growth. The studies reported in this paper were carried out on normal infants with the purpose of observing the extent and the duration of accumulation of surplus electrolyte in the body produced by a large increase in the level of intake and the effect of this excessive gain on the retentions of other electrolytes and on the distribution of body water. Such information should be relevant to the problem of correct replacement of electrolyte deficits incurred by processes of dehydration. The plan of study consisted in comparing retentions found over a fore-period with those produced by a large addition of the electrolyte under study to the food intake.

METHODS

Consecutive 24 hr. collections of urine and stools were obtained over the periods of observation by securing the infant comfortably on a "metabolism" bed. The quantity of milk mixture required for 4 days was prepared and the individual feedings were measured by volume and placed in separate nursing bottles which were then autoclaved and stored in a refrigerator. Accurate measurement of intake was obtained by weighing the bottles on a solution balance at the beginning and at the end of the 24 hr. periods. During the load periods the required amount of salt was measured by weight and placed in the 4 day quantity of the milk mixture. The daily intake thus measured as grams was converted to cubic centimeters, using the specific gravity determined for the milk mixture.

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TABLE 1

ESTIMATION OF UNMEASURED LOSSES
Infant W.M., 11-day period, wt. gain 243 gm.

	Na m.mol	Cl m.mol	K m.mol	N gm.
Balances found*	32.6	31.1	22.5	4.88
Theor. for wt. gain†	18.5	14.1	11.2	4.86
Unmeasured loss	14.1	17.0	11.3	0.02
Daily average UL	1.28	1.54	1.03	0.002

* Intake—Outgo in urine and stools
† Retention/gm. wt. gain: Na, 0.076 m.mol
Cl, 0.058 m.mol
K, 0.046 m.mol
N, 0.02 gm.
(From Camerer and Söldner's values for body content)

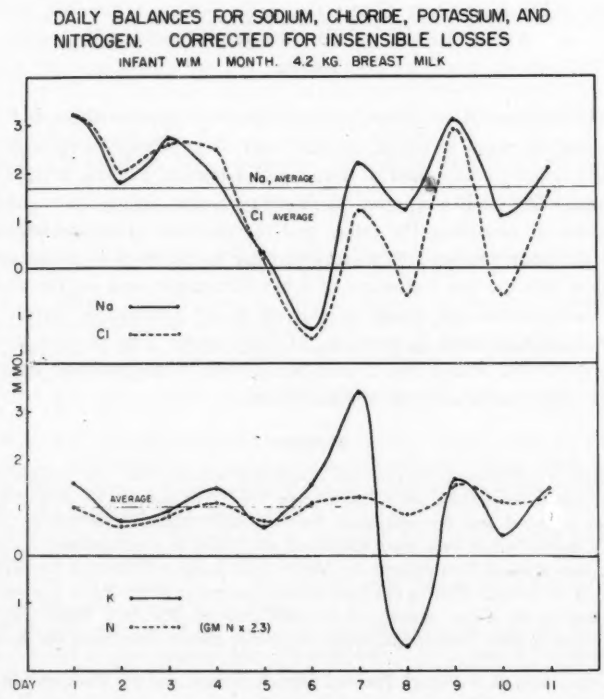

CHART 1

The infants were weighed at the beginning of each 24 hr. collection period on a specially rigged solution balance with a sensitivity of 2 parts in 1000 for weighings in the range encountered.

Sodium was determined by the Butler and Tuthill method[1] and potassium by the method of Shohl and Bennett[2] in the material from Infant C. The measurements were later repeated using the internal standard flame photometer[3] with excellent agreement. All the Na and K measurements from Infants W.M. and T. were obtained by flame photometry. Liquid specimens were, after appropriate dilution, analysed directly in flame photometer. Stools were prepared for analysis by digestion with nitric acid and filtering.[4] Measurements of Cl in urine, milk and in the stool filtrates was by the method of Wilson and Ball.[5] Serum was analysed for Cl by iodometric method of Sendroy[6] and for total CO_2 by the method of Van Slyke.[7] Serum pH was determined colorometrically using the Hastings and Sendroy bi-color standards.[8] The Kjeldahl method was used for nitrogen.[9]

Obstacles to Measurement of Electrolyte Balances

Since this plan of study rests on measurement of electrolyte balances, it is necessary to appraise the attainable accuracy of this measurement and here it has to be admitted that in spite of the excellent technics available for measuring intake in the food and outgo in the urine and stools, balance cannot be defined with desirable precision because of two obstacles: the loss of electrolytes by way of the skin, for which there is no practicable means of measurement, and a large oscillation of balance, which is apparently physiologic and which makes an extended period of observation necessary for dependable definition of the mean position of balance. These two obstacles are illustrated by data obtained over an 11 day period from a month old infant receiving breast milk, presented in table 1 and in chart 1. Estimations of the unmeasured losses of Na, Cl, K and N for the 11 day period were obtained by comparing the balances found by measuring intake and outgo in urine and stools and the theoretic retentions for the weight gain over the period derived from Camerer and Söldner's values for body content of newborn infants (table 1). The unmeasured losses of Na, Cl and K as defined by difference amount to approximately one half the retentions found by measuring intake and outgo in the urine and stools. According to these data, omission of this component of outgo produces values for retention which are about twice as large as they should be. The found and theoretic values for N are in close agreement and indicate that there was no appreciable loss by way of the skin.

The other bothersome feature of electrolyte balance, oscillation, is shown in chart 1, in which the day by day balances of Na, Cl, K and N over the 11 day period, corrected for unmeasured losses, are recorded. These estimations of actual balance were obtained by subtracting the daily average for UL (table 1) from daily balances found by measuring intake and outgo in the urine and stools. This correction for UL involves the assumption that it has a stationary value which should be approximately the case in the presence of fairly constant environmental circumstances. The daily balances estimated in this way for the extracellular electrolytes Na and Cl show a fairly close companionship, but they deviate widely from their mean values for the period. It will be seen that the trend of these deviations is progressively downward and then upward over periods of days. It is evident that a single 24 hour measurement of balance will have no significant relationship to the actual progress of growth. The daily balances found for the intracellular electrolytes, K and protein (N), show much smaller deviations from the mean for the period except for a single large oscillation of potassium balance. The position of this aberration of K on the chart suggests relation to the progressive decline of sodium balance. This chart illustrates the requirement for an extended period of observation to obtain a dependably average value for electrolyte balances.

TABLE 2

Day	Sodium Chloride Load								Infant C., aged 4 mo.							
	Na, m.mol.				Cl, m.mol.				K, m.mol.				N, gm.			
	Intake	Urine	Stools	Balance	Intake	Urine	Stools	Balance	Intake	Urine	Stools	Balance	Intake	Urine	Stools	Balance
1	86.8	17.9	0.5	+68.4	94.3	22.4	1.1	+70.8	29.4	23.9	1.5	+4.0	4.0	2.6	0.3	+1.1
2	86.8	92.4	0.5	− 6.1	94.3	97.1	1.1	− 3.9	29.4	21.7	1.5	+6.2	4.0	2.6	0.3	+1.1
3	86.8	95.4	0.5	− 9.1	94.3	105.5	1.1	+12.3	29.4	24.0	1.5	+3.9	4.0	1.9	0.3	+1.8
4	86.8	70.0	0.5	+16.3	94.3	77.0	1.1	+16.2	29.4	34.2	1.5	−6.3	4.0	2.7	0.3	+1.0
5	88.2	68.0	0.5	+19.7	95.9	71.3	1.1	+23.5	29.4	25.3	1.5	+2.6	4.0	2.6	0.3	+1.1
6	88.2	75.8	0.5	+11.9	95.9	81.0	1.1	+13.8	29.4	25.6	1.5	+2.3	4.0	2.2	0.3	+1.5
7	88.2	78.5	0.5	+ 9.2	95.9	83.8	1.1	+11.0	29.4	24.7	1.5	+3.2	4.0	2.4	0.3	+1.3
8	88.2	80.5	0.5	+ 7.2	95.9	87.0	1.1	+ 7.8	29.4	27.0	1.5	+0.9	4.0	2.4	0.3	+1.3
Total	700.0	578.5	4.0	+117.5	760.8	625.1	8.8	+126.9	235.2	206.4	12.0	+16.8	32.0	19.4	2.4	+10.2

Body wt.: Initial, 6869 gm. Final, 7140 gm. Gain, 271 gm.

TABLE 3

Day	Sodium Bicarbonate Load								Infant C., aged 7 mo.				N
	Na, m.mol.				Cl, m.mol.				K, m.mol.				
	Intake	Urine	Stools	Balance	Intake	Urine	Stools	Balance	Intake	Urine	Stools	Balance	Values for Period
1	92.8	55.8	1.7	+35.3	25.7	15.0	0.7	+10.0	29.4	28.7	2.3	−1.6	(8 days)
2	92.8	95.0	1.7	− 3.9	25.7	27.0	0.7	− 2.0	29.4	23.7	2.3	+3.4	gm.
3	92.8	101.0	1.7	− 9.9	25.7	27.0	0.7	− 2.0	29.4	31.7	2.3	−4.6	Intake, 31.8
4	92.8	71.5	1.7	+19.6	25.7	20.5	0.7	+ 4.5	29.4	21.7	2.3	+5.4	Urine, 24.0
5	92.8	85.1	1.7	+ 6.0	25.7	23.5	0.7	+ 1.5	29.4	29.7	2.3	−2.6	Stools, 3.9
6	92.8	71.1	1.7	+20.0	25.7	19.0	0.7	+ 6.0	29.4	26.7	2.3	+0.4	Balance, +3.9
7	92.8	75.7	1.7	+15.4	25.7	16.5	0.7	+ 8.5	29.4	22.5	2.3	+4.6	
8	92.8	96.9	1.7	− 5.8	25.7	29.0	0.7	− 4.0	29.4	23.7	2.3	+3.4	
Total	742.4	652.1	13.6	+76.7	205.6	117.5	5.6	+22.5	235.2	208.4	18.4	+8.4	

Body Wt.: Initial, 7699 gm. Final, 8070 gm. Gain, 371 gm.

TABLE 4

Day	Potassium Chloride Load								Infant C, aged 5 mo.							
	Na, m.mol.				Cl, m.mol.				K, m.mol.				N, gm.			
	Intake	Urine	Stools	Balance	Intake	Urine	Stools	Balance	Intake	Urine	Stools	Balance	Intake	Urine	Stools	Balance
1	18.4	9.6	0.9	+7.9	96.7	73.3	1.4	+22.0	100.0	78.6	4.1	+17.7	4.0	3.5	0.5	+0.0
2	18.4	15.7	0.9	+1.8	96.7	70.2	1.4	+25.1	100.0	69.7	4.1	+26.6	4.0	2.2	0.5	+1.3
3	18.4	8.5	0.9	+9.0	96.7	61.6	1.4	+33.7	100.0	77.9	4.1	+18.4	4.0	2.5	0.5	+1.0
4	18.4	21.4	0.9	−3.9	96.7	90.5	1.4	+ 4.8	100.0	90.0	4.1	+ 6.3	4.0	3.1	0.5	+0.4
5	18.4	11.1	0.9	+6.4	100.0	67.8	1.4	+30.8	104.0	75.9	4.1	+24.0	4.0	2.5	0.5	+1.0
6	15.8	12.0	0.9	+2.9	85.7	67.3	1.4	+17.0	89.0	85.9	4.1	− 1.0	3.4	2.4	0.5	+0.5
7	14.8	17.8	0.9	−3.9	80.3	79.1	1.4	+ 0.2	83.5	78.6	4.1	+ 0.8	3.2	2.5	0.5	+0.2
8	18.4	12.1	0.9	+5.4	100.0	99.8	1.4	− 1.2	104.0	107.3	4.1	− 7.4	4.0	2.2	0.5	+1.3
Total	141.0	108.2	7.2	+25.6	752.8	609.6	11.2	+132.4	782.1	663.9	32.8	+85.4	30.6	20.9	4.0	+5.7

Body Wt.: Initial, 7195 gm. Final, 7357 gm. Gain, 162 gm.

Effects of Electrolyte Loads

The subjects of these studies were two male infants in good nutritional status. Infant C was 4 months old and weighed 6869 gm. at the beginning of the first period of study. Infant T was 2 months old and weighed 2791 gm. The food intake was a mixture of evaporated milk, Karo syrup and water and the daily quantity was constant. The period of load for Infant C was eight days. The effects of loads of NaCl, KCl and $NaHCO_3$ were observed in separate periods of study. The load period for Infant T was four days followed by a four day after-period and the salts used in the two periods of study were KCl and K-acetate. In all the periods the electrolyte load was 10 m.mol./kg. body

TABLE 5

		Potassium Chloride Load								Infant M.T., aged 2 mo.							
		Na, m.mol.				Cl, m.mol.				K, m.mol.				N, gm.			
	Day	Intake	Urine	Stools	Balance	Intake	Urine	Stools	Balance	Intake	Urine	Stools	Balance	Intake	Urine	Stools	Balance
Load Period	1	8.9	11.5	0.2	−2.8	38.5	33.2	0.1	+ 5.2	40.7	29.7	2.8	+ 8.2	1.48	0.89	0.40	+0.19
	2	9.0	9.4	0.4	−0.8	38.7	32.4	0.2	+ 6.1	41.0	29.5	4.2	− 7.3	1.51	0.93	0.67	+0.09
	3	9.0	10.9	0.5	−2.4	38.7	27.6	1.2	+ 9.9	41.0	24.2	2.5	+14.3	1.41	1.02	0.30	+0.09
	4	9.3	7.5	0.2	+1.6	39.6	36.2	0.2	+ 3.2	41.3	33.2	3.6	+ 4.5	1.56	0.90	0.47	+0.19
	Total	36.2	39.3	1.3	−4.4	155.5	129.4	1.7	+24.4	164.0	116.6	13.1	+34.3	5.96	3.74	1.84	+0.38
After Period	1	9.1	4.6	0.8	+3.7	9.2	15.4	0.4	− 6.6	11.1	16.8	3.2	− 8.9	1.51	0.95	0.36	+0.20
	2	8.6	3.1	1.7	+3.8	9.8	5.9	0.2	+ 3.7	10.9	3.7	3.7	+ 3.5	1.44	0.43	1.19	−0.18
	3	8.1	4.8	0.0	+3.3	8.2	7.8	0.0	+ 0.4	10.2	8.1	0.0	+ 2.1	1.34	0.73	0.00	+0.61
	4	8.5	5.7	0.3	+2.5	8.7	9.2	0.2	− 0.7	10.7	4.5	3.3	+ 2.9	1.31	0.53	0.77	+0.01
	Total	34.3	18.2	2.8	+13.3	35.9	38.3	0.8	− 3.2	42.9	33.1	10.2	− 0.4	5.60	2.64	2.32	+0.64

Body Wt.: Load period: Initial, 2791 gm. Final, 2886 gm. Gain, 95 gm.
After period: Initial, 2886 gm. Final, 2982 gm. Gain, 96 gm.

weight/day. This load is approximately equivalent to the quantity of NaCl ordinarily used in the treatment of severe diarrheal dehydration. The measurements of daily intake and outgo in the urine and stools and the resulting values for balance for Na, Cl, K and N are given in tables 2 to 6.

Correction of these data for unmeasured losses of the electrolytes was undertaken on the basis of values found over periods preceding the addition of the load to the food intake. Unfortunately at the time these studies were carried out the importance of prolonged fore-periods was not appreciated. The periods were much too short for definition of a dependably average value for apparent retentions or for derivation of theoretic retentions from observed body weight gain. Moreover body weight gain over the periods of load cannot be used to derive retentions referable to growth because of the influence of the electrolyte loads on the water balance of the body. It was therefore necessary to derive the theoretic retentions for growth on the basis of statistically expected values for the rate of body weight gain of healthy infants in relation to age. This rate of weight gain, which declines extensively over the early months of infancy, is shown by the broken line in chart 2. Using the expected weight gain for age, the theoretic gains for the electrolytes are derived from Camerer and Söldner's values for body content.[10] Obviously retentions for growth by the individual infant found by this statistical

TABLE 6

		Potassium Acetate Load								Infant C., aged 3 mo.							
		Na, m.mol.				Cl, m.mol.				K, m.mol.				N, gm.			
	Day	Intake	Urine	Stools	Balance	Intake	Urine	Stools	Balance	Intake	Urine	Stools	Balance	Intake	Urine	Stools	Balance
Load Period	1	11.5	5.2	0.4	+5.9	12.1	10.9	0.3	+ 0.9	42.6	29.5	1.6	+11.5	2.09	1.02	0.22	+0.85
	2	11.9	12.0	0.4	−0.5	12.5	11.8	0.3	+ 0.4	43.9	40.8	1.6	+ 1.5	2.09	1.20	0.22	+0.67
	3	11.5	10.5	0.4	+0.6	12.0	9.6	0.3	+ 2.1	42.3	39.1	1.6	+ 1.6	2.09	0.73	0.22	+1.14
	4	11.9	9.4	0.4	+2.1	12.5	9.2	0.3	+ 3.0	43.9	35.4	1.6	+ 6.9	2.09	0.68	0.22	+1.19
	Total	46.8	37.1	1.6	+8.1	49.1	41.5	1.2	+ 6.4	172.7	144.8	6.4	+21.5	8.36	3.63	.88	+3.85
After Period	1	11.8	9.2	0.7	+1.9	12.4	4.7	0.5	+ 7.2	13.5	14.3	0.7	− 1.5	2.09	0.84	0.28	+0.97
	2	11.6	8.0	0.7	+2.9	12.2	10.1	0.5	+ 1.6	13.3	10.6	0.7	+ 2.0	2.09	0.94	0.28	+0.87
	3	11.3	7.6	0.7	+3.0	11.9	9.0	0.5	+ 2.4	13.0	10.8	0.7	+ 1.5	2.09	1.15	0.28	+0.66
	4	11.6	6.6	0.7	+4.3	12.2	8.2	0.5	+ 3.5	13.2	8.3	0.7	+ 4.2	—	—	—	—
	Total	46.3	31.4	2.8	+12.1	48.7	32.0	2.0	+14.7	53.0	44.0	2.8	+ 6.2	6.27	2.93	0.84	+2.50

Body Wt.: Load period: Initial, 3191 gm. Final, 3387 gm. Gain, 196 gm.
After period: Initial, 3387 gm. Final, 3501 gm. Gain, 114 gm.

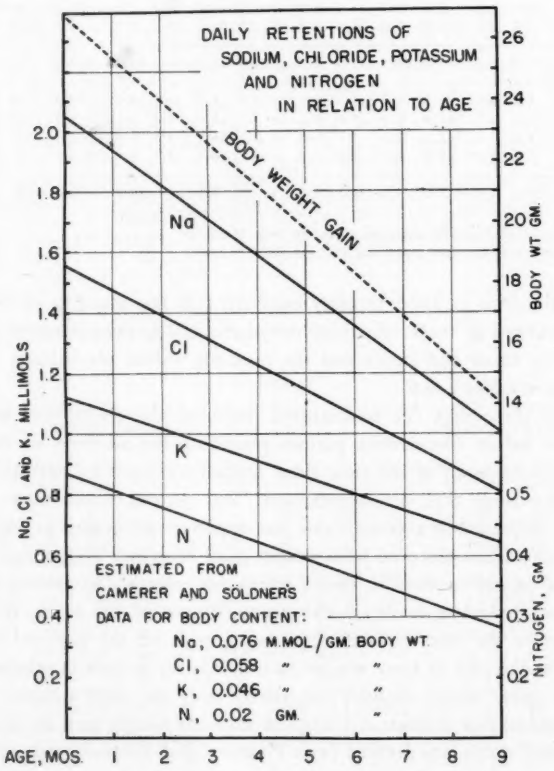

CHART 2

approach must be regarded as rough approximations. It is, however, necessary to use them in order to obtain some abatement of the large error in balance measurement produced by unmeasured losses. The estimations of these losses in the fore-periods are given in table 7. There is wide discrepancy between the values found for UL in the two fore-periods from Infant C. This is probably to some extent referable to the short periods. It is also to be noted that the eight day fore-period for Infant T was not continuous but was composed of three separate periods of 3, 2 and 3 days, respectively, and the intervals between the periods were 4 and 3 weeks. The values derived for UL

TABLE 7

ESTIMATIONS OF UNMEASURED LOSSES; LOAD EXPERIMENTS
Values average/day

		Na	Cl	K	N
		m.mol	m.mol.	m.mol.	gm.
Infant C	Fore-period (4 days), retentions found	6.9	9.5	3.7	1.31
NaCl and	Theoretic retentions for growth	1.5	1.2	0.9	0.42
KCl periods	Unmeasured losses	5.4	8.3	2.8	0.89
Infant C	Fore-period (3 days), retentions found	1.2	0.8	2.4	0.16
$NaHCO_3$	Theoretic retentions for growth	1.2	0.9	0.7	0.34
period	Unmeasured losses	0.0	0.0	1.7	0.0
Infant T	Fore-period (8 days), retentions found	3.0	3.4	2.9	0.49
KCl and	Theoretic retentions for growth	1.8	1.4	1.1	0.48
K-acetate periods	Unmeasured losses	1.2	2.0	1.8	0.01

Retentions found: Intake-outgo in urine and stools.
Theoretic retentions for age from chart 1.

obtained by combining these periods approximate those found for the breast-fed Infant W.M. (table 1). The fore-periods for Infant C were so far apart in time—four months—that it was decided not to combine them. Except in the first period for Infant C the observed retention of N did not exceed the theoretic gain for growth.

The average daily values for the unmeasured losses given in table 7 were subtracted from the observed daily balances for the corresponding periods recorded in tables 2 to 6. The daily values for actual retention obtained by this rough process of estimation are recorded additively in the first sections of charts 3 to 7. For comparison, the theoretic retentions for growth are shown by thin lines. The charts describe the large accumulation in the body of the electrolytes contained in the load. Adjustment to the load is very gradual; not until almost the end of the eight day periods is there a beginning of removal of the surplus of electrolytes. The magnitude of these additions of electrolyte to the body over the eight day periods is best appraised by referring them to an estimated initial body content. In this term, the retention of Na at the end of the NaCl period was 15% and the gain of K over the KCl period was 18%. In the sodium chloride and sodium bicarbonate periods (Infant C) there is a curious spurt of removal on the second and third day which, however, is not sustained. The long lag in adjust-

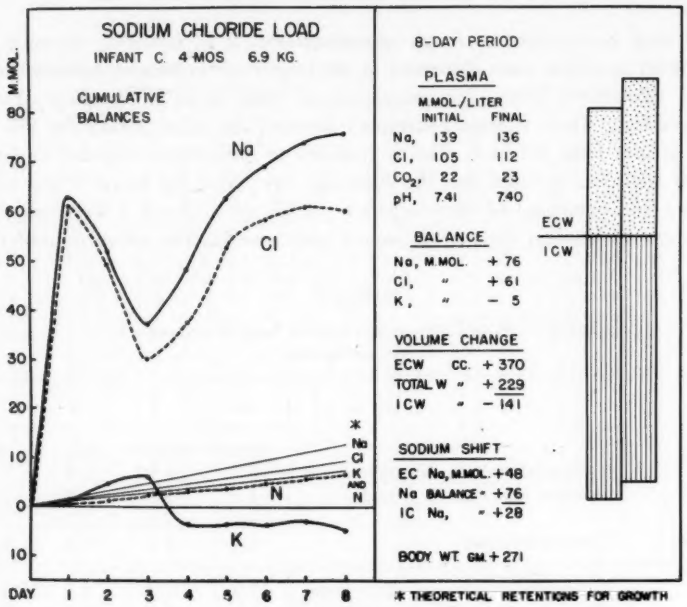

CHART 3

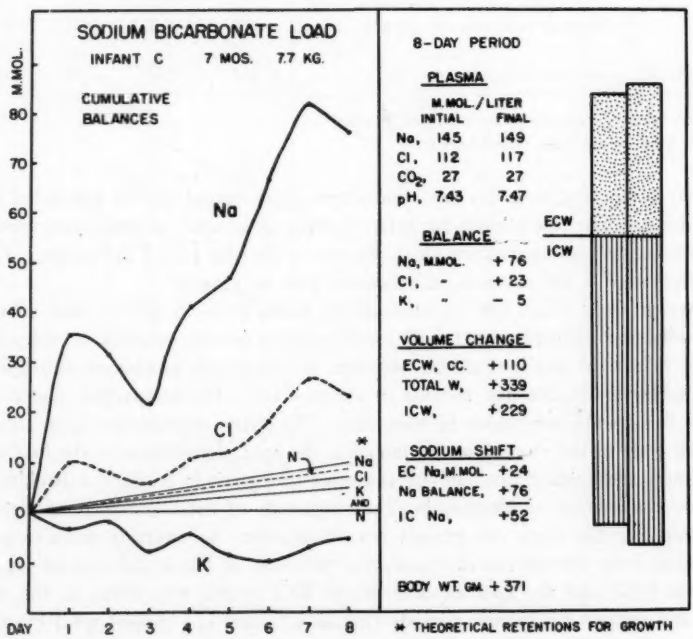

CHART 4

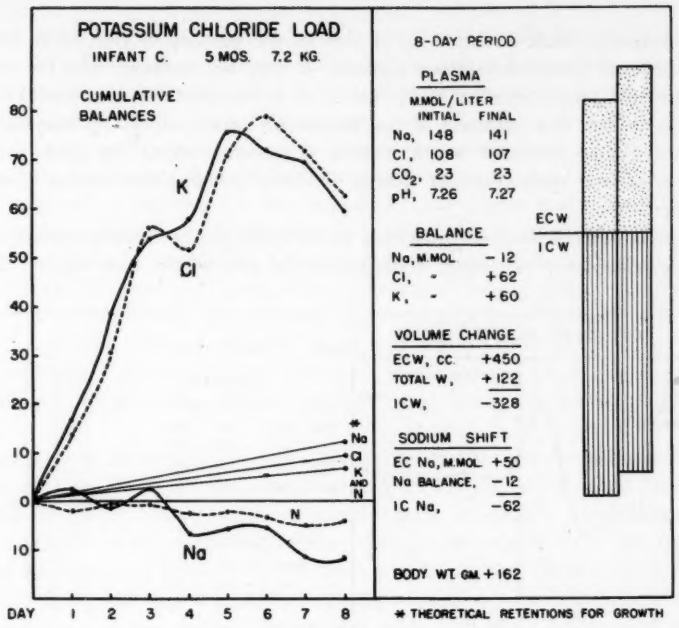

CHART 5

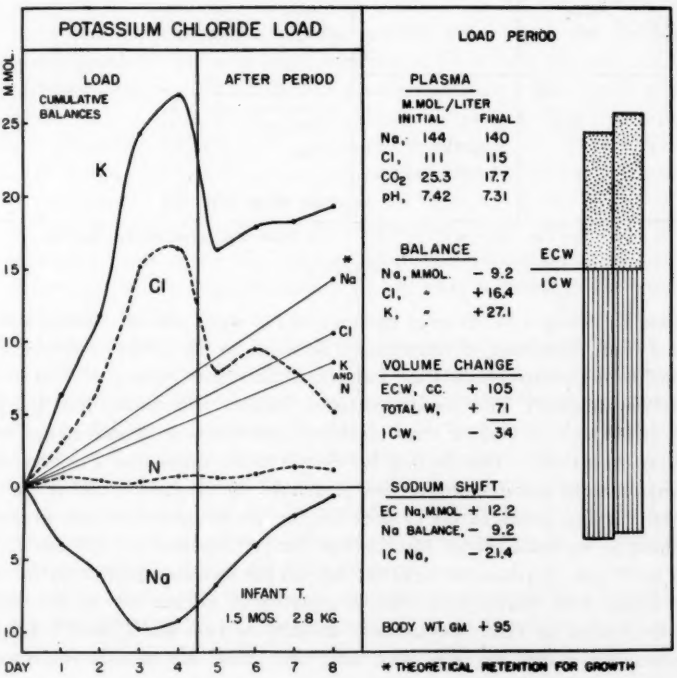

CHART 6

ment of outgo to intake is surprising in view of the quantity of electrolytes which the daily volume of glomerular filtrate contains. It may be estimated that for the NaCl period, Infant C, daily filtration of Na and of Cl by the glomeruli is about 40 times the load. It is evident that response of the mechanism which adjusts reabsorption to the requirement for an increased rate of removal is extremely slow. The charts make clear the hazard of over-replacement of deficits of electrolytes in the treatment of diarrheal dehydration.

The charts describe another prominent and physiologically important effect of load: an inverse relationship of change in balance of the extracellular base Na and the intra-

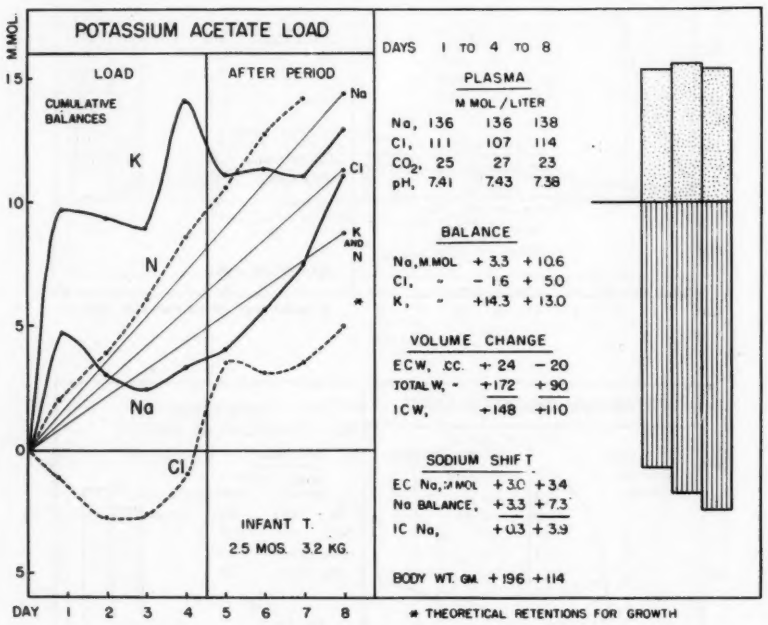

CHART 7

cellular base K. Along with the large retention of Na under sodium chloride and sodium bicarbonate loads, reduction of retention of K occurs to the extent of producing actual deficits and in the potassium chloride and potassium acetate periods of load loss of Na from the body is found. This sodium-potassium balance relationship was first observed by Bunge in 1873 on the basis of short ingestion experiments using sodium and potassium bicarbonates or citrates.[11] This finding led Bunge to the thesis that a correct Na/K intake is important in animal nutrition and is defined by the ratio found in the milk of the species.[12] It also produced the premise for the use of potassium salts as diuretics in the treatment of nephritic edema. MacKay and Butler[13] reported in 1932 that administration of 5 to 10 gm. of potassium chloride/day did not increase significantly the excretion of Na or edema fluid. Recently the effect of ingestion of sodium salts on the excretion of K has been studied in three normal adult subjects by Leaf and Couter.[14] Large loads, approximately 10 m.mol./kg./day were used over three day periods following a low

fore-period intake of NaCl. It was found that a sodium chloride load did not appreciably alter the outgo of K in the urine but that when sodium acetate was given a large increase of potassium excretion occurred. In a single subject studied by one of the authors (J.L.G.),[15] a load of NaCl, 20 gm. daily for three days, following a fore-period in which a usual intake was provided produced a large increase of potassium removal. The absence of this effect in the NaCl experiments of Leaf and Couter might relate to the initial deficit of body Na produced by the very low fore-period intake. Evidence that a NaCl load will cause an increased removal of K from the body under the circumstance of fasting has been found in studies on the life raft ration by Butler and one of the authors (J.L.G.).[16] The loss of Na in the urine which is incidental to the state of fasting can be reduced to about one half by a moderate intake of NaCl but at the cost of a large extension of K deficit. The same effect was observed when sea water was drunk within the limits of gastrointestinal tolerance. According to chart 3, a NaCl load following a usual intake produces in a normal infant a potassium deficit of about the same extent as found for the $NaHCO_3$ period.

The balances for the intracellular ion, protein, are recorded on the millimol ordinate of the charts as gm. N $\times$ 2.3 in order to compare them with the potassium balances on the basis of the relative values for body content of these two mainly intracellular electrolytes. As regards change in protein balance, there is the consideration that this component of the electrolyte structure of cell fluid is not diffusible. With a fixed intake a change of balance will therefore involve an alteration of protein metabolism and this implies mediation beyond osmotic mechanisms. Over the NaCl load period nitrogen balance was not disturbed by a deficit of K; retention corresponded closely with the theoretic gain for growth. When the load was composed of Na without Cl (chart 4), nitrogen gain went considerably above the growth requirement. In the KCl load periods (charts 5 and 6), the very large retention of Cl without Na was accompanied by depression of nitrogen retention so that a wide discrepancy developed between the balances for K and its intracellular anion companion, protein. The charts suggest a relationship between Na deficit and depression of nitrogen retention which openly beckons to the adrenal gland for explanation. However, in the K-acetate period, in the presence of reduction of Na retention, nitrogen retention was found extensively above the expected gain for growth, under the circumstance of a large deficit of Cl instead of the huge retentions found in the KCl periods. So there is intimation of an inverse relationship between the balances for the anions, Cl and protein, except in the instance of a Cl load accompanied by Na.

In contrast with these puzzling findings for the anions, an inverse balance relationship for the cations Na and K was found in all the load periods. An implication in relation to the distribution of body water is that an extracellular volume increase produced by a sodium load will be accompanied by reduction of the volume of intracellular fluid. A potassium load will be expected to cause the reverse change in the volume of the body fluids. Here, however, there is the consideration that the volume changes may be modified by a shift of Na to or from the intracellular compartment. So that in a study of effects of electrolyte loads, an attempt to measure volume changes of the body fluids including influence of sodium shift is clearly commanded.

Approach rests on faith in the exclusively extracellular position of Cl. On this premise Darrow[17] has devised a process of estimation which is illustrated in table 8 using data from the sodium bicarbonate load period. The measurements required are the plasma

concentrations of Na and Cl at the beginning and end of the period and the change in their balances over the period. The concentrations found in the plasma are corrected for extracellular fluid as a whole by the factors given in the table. Measurement of body weight at the beginning and end of the period is also required. Initial extracellular fluid volume is taken as 25% of initial body weight. Change in volume is then computed on the basis of change in Cl content and final Cl concentration as shown in the table.

TABLE 8

ESTIMATION OF VOLUME CHANGE OF BODY FLUIDS AND OF SODIUM SHIFT

Data from Infant C, 8 kg. $NaCHO_3$ load. 8 day period.		
Plasma values, m.mol./l.:		
Cl: Initial, $101\times1.11=112$	Final, $105.5\times1.11=117$	
Na: Initial, $142\times1.02=145$	Final, $146\times1.02=149$	
Balance for period: Cl, +23 m.mol. Na, +76 m.mol.		
Body Wt. gm., Initial, 7700. Final, 8070.		
	Volume Change	
Initial EC volume,	$7700\times0.25=1920$ cc.	
Initial EC Cl,	$1.92\times112=$ 215 m.mol.	
Final EC Cl,	$215+23=$ 238 m.mol.	
Final EC volume,	$238+0.117=2030$ cc.	
EC volume,		+110 cc.
* Total body water,		+339 gm.
IC volume,		+229 cc.
	Sodium Shift	
Initial EC Na;	$1.92\times145=278$ m.mol.	
Final EC Na;	$2.04\times149=302$ m.mol.	
EC Na		+24
Na Balance		+76
IC Na		+52

* Wt. gain—0.25 × theoretic for age.

Change in total body water is estimated by subtracting from body weight gain 25% of the theoretic gain for age (chart 2), and change in intracellular fluid volume is defined by difference. Measurement of sodium shift rests on the values found for initial and final extracellular fluid volume by way of the chloride data. The steps are shown in the table.

In the second section of the charts, the plasma data, the electrolyte balances and body weight changes found for the period and the derived data for volume change and sodium shift are recorded. A perspective view of volume change is provided by the diagram. Initial values are shown by the first column, taking ECW as 25% and ICW as 50% of initial body weight. The effects of the various loads will be noted separately.

Sodium Chloride Load, Infant C (chart 3): The large addition of Na to the body beyond the theoretic gain for growth produces, as would be expected, increase of the volume of extracellular fluid. Initial plasma (Na) is approximately preserved but there

is a considerable rise of Cl. The increase of ECW volume derived from the Cl data is not of an extent to contain all the Na retained at the level found in the plasma. As shown by the sodium shift data, increase of plasma (Na) is prevented by transfer of one third of the Na gain to the intracellular compartment. This addition to IC Na is much larger than the loss of K and would be expected to produce some increase of ICW. According to the estimations of volume change there is a loss of ICW, so that there is, in this respect, discrepancy between estimated volume change and sodium shift data.

Sodium Bicarbonate Load, Infant C (chart 4): Effects of the electrolyte balance changes shown in first section of the chart, if confined to extracellular fluid, should be a large expansion of volume and a large extension of the concentration of bicarbonate. The negative balance for K would be expected to cause some reduction of intracellular fluid volume. The estimations of volume change describe increase of ECW but also a twice as large increase of ICW and there was no alteration of the initial values for plasma bicarbonate or pH. Explanation is provided by the sodium shift data. Two-thirds of the large sodium gain to the body was transferred to the intracellular compartment. The large excess of Na retention over the small Cl gain is thus removed from extracellular fluid and extension of bicarbonate is prevented. These findings sustain Darrow's hypothesis that sodium shift may operate as a defense against alkalosis.[18] They also provide a striking illustration of effect of sodium shift on distribution of body water. This stowing of surplus Na in the intracellular compartment as a process of defense of extracellular pH and the resulting expansion of ICW together with some removal of K in order to meet the requirement for osmolar equality between the body fluids provides an explanation for the development of K deficit under a $NaHCO_3$ load. There is no such evident premise for expecting that a NaCl load would produce the transfer of Na and loss of K recorded in chart 3.

Potassium Chloride Load, Infant C (chart 5): Here the body fluid mechanisms are presented with the interesting problem of how to deal with a load composed of an intracellular base and an extracellular acid radical. The retentions of K and of Cl were equally large. As shown by the estimations of volume change, Cl does not need the companionship of Na to command the volume of extracellular fluid. Expansion of ECW to contain the large retention of Cl was so accurately accomplished that initial plasma (Cl) was not altered. This increase of volume together with actual deficit of Na would be expected to greatly lower (Na) and incidentally cause extensive reduction of the bicarbonate concentration. At the end of the period plasma (Na) was found to be reduced to only a small extent and the initial values for CO_2 and pH were preserved. Explanation is again provided by the sodium shift data. Sodium was taken from the intracellular compartment to an extent which provided an addition to extracellular Na, in the presence of actual loss of Na from the body, which is almost equal to the large Cl retention with resulting prevention of bicarbonate reduction. Sodium shift is thus found to be capable of providing defense against acidosis from Cl excess in extracellular fluid as well as against alkalosis from Na excess, as shown in the preceding chart.

The large transfer of Na to extracellular fluid is approximately equal to K retention. Total intracellular base is therefore not appreciably altered so that little or no change in intracellular fluid volume would be expected, in spite of the large addition of K to the body. The estimations of volume change describe an actual reduction of ICW. In spite of this discrepancy between the sodium shift and volume change data, the main effects of a KCl load are satisfactorily indicated. The loss of Na is explained by a larger with-

drawal from the intracellular compartment than is required to cover the accumulation of Cl in extracellular fluid.

Potassium Chloride Load, Infant T (chart 6): A second set of observations of the effects of a KCl load were obtained from the younger infant, T. The period of load was four days. Unfortunately plasma data were not obtained at the end of the after period. The findings are in their main features the same as those from Infant C. As shown by the measurements of plasma CO_2 and pH, complete defense against acidosis by sodium shift was not attained at the end of the four day period of load. The shift was, however, of sufficient extent to prevent acidosis of disastrous degree.

TABLE 9

BALANCES ABOVE OR BELOW FORE-PERIOD; VALUES AVERAGE/DAY

Subject	Load	Na m.mol.	Cl m.mol.	K m.mol.	N gm.
C 8 days	NaCl	+7.8	+6.4	−1.6	−0.02
	$NaHCO_3$	+8.4	+2.0	−1.3	+0.33
	KCl	−3.7	+7.0	+7.0	−0.60
T 4 days	KCl	−4.1	+2.7	+4.3	−0.39
	K-acetate	−2.0	−2.6	+2.5	+0.47

These findings suggest that KCl is not a suitable salt to use for replacement of loss of intracellular fluid incurred by dehydrating processes. Although repair of a deficit of K should be gained, owing to withdrawal of Na, little or no restoration of intracellular fluid volume can be expected.* According to these data, KCl would not be expected to remove edema fluid. Although Na may be withdrawn from the body, there is actual addition of Na to extracellular fluid and expansion of volume produced by the large addition of Cl.

Potassium Acetate Load, Infant T (chart 7): By using an oxidizable anion a load of K alone was provided. In the absence of the interfering effects of Cl, retention of K produces expansion of intracellular fluid volume. No appreciable change in extracellular fluid volume was found in spite of depression of the retentions of Na and Cl. This is explained by the reduction of plasma (Cl) found at the end of the load period which also produced in the presence of stationary (Na) and absence of Na shift a small extension of bicarbonate. In the after-period these changes were reversed in the presence of considerable replenishment of Na and Cl but without appreciable removal of surplus K. As shown in the chart, the balance changes are much smaller in relation to theoretic retentions for growth than were found for a KCl load (chart 6). The derived data are, however, consistent and may be taken as describing the main effect of load as expansion of intracellular fluid volume in direct relation to K retention.

* This statement applies only to the use of K and Cl alone. If Na is not provided, intracellular Na will presumably not be withdrawn and the addition of K to intracellular fluid should then cause corresponding increase of volume. In Darrow's solution, for instance, Cl is covered by Na and K is, in effect, provided with an oxidizable anion, i.e., as K-lactate, and should therefore produce expansion of intracellular fluid volume as found in the K-acetate load experiment.

The average daily values for observed retentions of the individual electrolytes over the load periods (tables 2-6) above or below the average observed values found in the fore-period (table 7) are recorded in table 9 with the purpose of describing alterations of retention directly referable to load; i.e., the component of retention produced by growth is not included. The changes in retention measured on this basis and recorded in the table are in agreement as regards direction with those noted in charts 3 to 7.

Summary

The effects of large electrolyte loads provided by adding various salts to a constant food intake were observed in two healthy infants on the basis of balance measurements found over a fore-period.

The salts used were NaCl, $NaHCO_3$, KCl and K-acetate. The balances found over the periods of load were corrected for unmeasured loss by a value derived from the observed fore-period balances and an estimation of actual retention for growth based on expected body weight gain in relation to age. The measurements of balance thus obtained are regarded as rough approximations. It is believed, however, that they permit a description of the following main features of effects of load.

Adjustment of outgo to load was found to be a gradual process. Accumulation of surplus electrolyte in the body continued almost to the end of eight day periods of load and amounted to about 15% of initial body content.

With the large retentions of Na produced by NaCl or by $NaHCO_3$, extensive depression of K retention below the fore-period level was found. The inverse effect, reduction of Na retention in the presence of large gain of K, was observed in the KCl and K-acetate periods.

Nitrogen retention was not disturbed by NaCl load and was found above the fore-period rate in the $NaHCO_3$ and K-acetate periods but was extensively depressed by KCl.

Using the balance data and measurements of the concentration of Na and Cl in the blood plasma, estimations of sodium shift were obtained by the method of Darrow. A large transfer of Na to the intracellular compartment was found in the $NaHCO_3$ period and in the KCl period Na was extensively removed. These transfers of Na closely preserved the usual concentration of bicarbonate in the plasma in the presence of widely unequal retentions of Na and Cl. A considerable gain of intracellular Na was observed under the NaCl load, but no removal was found in the K-acetate period.

Estimations of volume change of extracellular and of intracellular fluid are presented which illustrate the large effect of sodium shift in determining the distribution of body water accompanying electrolyte balance changes produced by load.

References

1. Butler, A. M., and Tuthill, E., Application of uranyl zinc acetate method for determination of sodium in biological material, J. Biol. Chem. **93**:171, 1931.
2. Shohl, A. T., and Bennett, H. B., Micro-method for determination of potassium as iodoplatinate, J. Biol. Chem. **78**:643, 1928.
3. Berry, J. W., Chappell, D. G., and Barnes, R. B., Improved method of flame photometry, Indust. & Engin. Chem. (Anal. Ed.) **18**:19, 1946.
4. Lowry, O. H., and Hastings, A. B., Histochemical changes associated with ageing, J. Biol. Chem. **143**:257, 1942.
5. Wilson, D. W., and Ball, E. G., Study of estimations of chloride in blood and serum, J. Biol. Chem. **79**:221, 1928.

6. Van Slyke, D. D., and Hiller, A., Application of Sendroy's iodometric chloride titration to protein containing fluids, J. Biol. Chem. **167**:107, 1947.
7. Van Slyke, D. D., and Neill, J. M., Determination of gases in blood and other solutions by vacuum extraction and manometric measurement, J. Biol. Chem. **61**:523, 1924.
8. Hastings, A. B., and Sendroy, J., Jr., Colorometric determinations of blood pH at body temperature without buffer standards, J. Biol. Chem. **61**:695, 1924.
9. Campbell, W. R., and Hanna, M. I., Determination of nitrogen by modified Kjeldahl method, J. Biol. Chem. **119**:1, 1937.
10. Camerer, W., Jr., and Söldner, Die chemische Zusammensetzung des neugeborenen, Ztschr. f. Biol. **39**:173, 1900; **40**:529, 1900; **43**:1, 1902.
11. von Bunge, G., Über die Bedeutung des Kochsalzes und das Verhalten des Kalisalz in menschlichen Organismus, Ztschr. f. Biol. **9**:104, 1873.
12. Shohl, A. T., Mineral Metabolism, American Chemical Society, Monograph Series no. 82, New York, Reinhold Publishing Corporation, 1939.
13. MacKay, E. M., and Butler, A. M., Studies of sodium and potassium metabolism, J. Clin. Investigation **14**:923, 1935.
14. Leaf, A., and Couter, W. T., Some effects of variation of sodium intake and of different sodium salts in normal subjects, J. Clin. Investigation **28**:1082, 1949.
15. Gamble, J. L., Chemical Anatomy, Physiology and Pathology of Extracellular Fluid, Cambridge, Mass., Harvard University Press, 1949, chart 33.
16. Gamble, J. L., Physiological information from studies on life raft ration, The Harvey Society Lectures, Series 42, Lancaster, Pa., Science Press Printing Company, 1947, p. 247.
17. Darrow, D. C., Retention of electrolyte during recovery from severe dehydration due to diarrhea, J. Pediat. **28**:515, 1946.
18. Darrow, D. C., Schwartz, R., Iannucci, J. F., and Coville, F., Relation of serum bicarbonate concentration to muscle composition, J. Clin. Investigation **27**:198, 1949.

SPANISH ABSTRACT

Efectos de Excesos de Electrolitos

Los efectos de la ingestión de varias sales de sodio y potasio en la retención de electrolitos y en la distribucion del agua del cuerpo fueron estudiados en niños con crecimiento normal. Se observó que el ajuste renal siguiente a la ingestion elevada de sales, se realiza lentamente, lo que resultó en la retención de grandes cantidades de los electrolitos añnadidos a la dieta, durante un periódo de estudio de ocho días. Se encontró, que un aumento en la retención del sodio fue acompañado por una reducción en la retención del potasio, y el efecto reverso sé obtuvo cuando el potasio fué admistrado. Durante la administración del bicarbonato de soda, una gran parte del sodio retenido fué transferido al compartimiento intracelular; mientras que la administración de cloruro de potasio produjo el desplazamiento del sodio intracelular. Estos intercambios (shifts) de sodio evita alteraciones del bicarbonato del plasma en presencia de retenciones variables de sodio y cloruros. En relación al tratamiento de la deshidratación con agua y electrolitos, los resultados de estos estudios indican el peligro de la "sobrehidratacion," particularmente, si el tratamiento es continuado después del replazamiento de las perdidas de fluido del cuerpo. Asimismo, indican que el uso excesivo de soluciones de cloruro de sodio o bicarbonato de sodio pueden agravar una deficiencia potasica existente.

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TOTAL BODY WATER IN CHILDREN

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ALTHOUGH extensive studies of body fluid physiology in children have been made over the past 50 years, few measurements of total body water have been reported. This has not been due to lack of realization of the importance of this over-all dimension of the body fluids, but to lack of a suitable method applicable to the living subject. The recent availability of deuterium oxide for laboratory use has provided a practicable means of in vivo measurement.[1] There is also now at hand the antipyrine method devised by Brodie et al.[2,3] Deuterium oxide is an ideal tracer for water, is nontoxic at low concentrations and can be used to study the dynamics of water distribution. An additional advantage is that repeated determinations can be made in the same individual at any time interval. The disadvantage of the method is that special apparatus, which is not available in many laboratories, is required. For this reason comparison of results obtained by the two methods is desirable. The disadvantages of the antipyrine method are that it may be less accurate because of slight binding by protein and the allowance which must be made for its rate of metabolism. Also certain substances, some of which may be used in studying renal function or extracellular fluid volume (sulphadiazine, sodium thiosulphate and sodium para-aminohippurate), interfere with the antipyrine measurement and, therefore, cannot be employed simultaneously with it. A minor limitation is that an interval of four days must elapse before it can be repeated.

In this study measurements of total body water in infants and children were made by both of these methods simultaneously, using blood taken by finger or heel puncture. To this end it was necessary to devise a micro-modification of the antipyrine method which is described below. The subjects of this study were essentially normal as regards nutritional and body fluid status at the time the measurements were made. The reasons for their presence in hospital are recorded in table 1.

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Procedure

Antipyrine (1-phenyl-2,3-dimethylpyrazalone-5-one) was dissolved in 99.8% deuterium oxide and the solution autoclaved in sealed ampoules. 1.5 ml./kg. body weight of the deuterium oxide containing antipyrine 13 mg./ml. was injected intravenously and the time noted. (If the total body water were to be determined only by the antipyrine method, the antipyrine would be dissolved in pyrogen-free distilled water to a concentration of 20 mg./ml.) The amount injected was determined by taking the difference in weights of the syringe before and after injection, and calculating the volume from the known density of the solution. Any error in administration affected both determinations equally.

TABLE 1

Comparison of Age, Sex, Weight, Height and Surface Area to Total Body Water as Determined by Deuterium Oxide and Antipyrine Methods

Age yr.	Sex	Condition	Wt. kg.	Ht. cm.	Surface area sq. m.	body water l.		Difference l.	Mean l.	Body water as % body wt.
						D_2O	Antipyrine			
1/365	M	Full term	2.95	48	0.190	2.29	2.35	0.06	2.32	78.6
3/365	F	Full term	4.03	53	0.230	3.18	3.17	0.01	3.18	78.8
9/365	M	Premature	1.93	48	0.155	—	1.53	—	—	79.0
15/365	F	Premature	2.27	48	0.170	1.67	1.60	0.07	1.64	72.2
16/365	F	Premature	2.38	46	0.165	1.71	1.63	0.08	1.67	70.2
21/365	M	Premature	2.27	47	0.165	1.89	—	—	—	83.0
4/52	M	Harelip	4.19	56	0.240	3.05	2.88	0.17	2.97	70.8
5/52	M	Harelip	5.34	58	0.280	3.52	3.36	0.16	3.44	62.2
6/52	M	Harelip	5.47	58	0.280	3.71	3.39	0.32	3.55	64.9
8/52	M	Harelip	5.12	59	0.275	3.49	3.45	0.04	3.47	67.8
3/12	M	Tetany	4.88	57	0.260	3.08	3.00	0.08	3.04	62.3
4/12	M	Postmeningitis	6.80	64	0.330	4.82	4.81	0.01	4.82	70.7
9/12	M	Convalescent pneumonia	10.80	75	0.450	6.15	5.97	0.18	6.06	56.2
9/12	F	Mentally defective	8.22	70	0.385	4.36	4.38	0.02	4.37	53.2
1 3/12	F	Convulsions	11.40	79	0.480	6.46	6.80	0.34	6.63	58.2
1 4/12	M	Convulsions	10.15	76	0.450	5.90	5.96	0.06	5.93	58.5
2 2/12	M	Suspected intussusception	13.10	88	0.540	8.00	7.53	0.47	7.77	59.3
2 2/12	M	Cleft palate	12.66	90	0.550	7.40	6.65	0.75	7.03	55.6
3 10/12	M	Contracture	15.11	104	0.660	9.50	—	—	—	62.8
4	M	Convulsions	16.60	99	0.660	9.15	—	—	—	55.2
4 2/12	M	Mentally defective	15.00	—	0.610	8.83	8.64	0.19	8.74	58.3
7 1/12	F	Cleft palate	16.83	115	0.750	10.23	9.74	0.49	9.99	59.3
7 9/12	M	Suspected fracture	27.40	126	0.970	16.20	15.50	0.70	15.85	57.9
10 10/12	M	Naevus	36.65	142	1.210	19.00	20.10	1.10	19.55	53.4

Control, 2, 3 and 5 hr. samples of blood were obtained from finger or heel punctures in 4 x 100 mm. glass tubing, as described by Davies[4] for micro-Hinton analyses. The specimens were centrifuged at 2000 rpm. for 20 min. A file scratch was made at the serum-cell junction, the tube snapped at this point, and the portion containing the serum capped at both ends and kept for analysis. From 0.15 to 0.2 ml. serum was obtained from each tube.

The deuterium oxide concentration in serum water was determined by the falling drop method (Schloerb et al.[5]). The total body water was calculated from the concentration in the 2 and 3 hr. samples, by which time equilibrium was reached.

The antipyrine determinations were made in duplicate on the control, 2, 3 and 5 hr. samples by the micro-method described below. Serum instead of heparinized blood was used.

Reagents: 1. Zinc sulfate reagent. 100 gm. of $ZnSO_4 \cdot 7H_2O$ and 40 ml. sulfuric acid are dissolved in water and diluted to 1 l. 2. 0.75 N sodium hydroxide. 3. 4 N sulfuric acid. 4. 0.2% sodium nitrite solution.

Standards: Prepare standards from a stock solution of antipyrine in water containing 100 mg./l.

Use working standards ranging from 4 to 10 μg/ml. by making appropriate dilutions of the stock in water. Run a standard curve with each set of determinations.

Protein precipitation: Use Van Slyke "between-the-lines" Shohl-tipped pipettes to deliver the water, zinc reagent and sodium hydroxide. Use Folin type pipettes to deliver the serum samples. Into each 40 x 12 mm. tube, deliver 0.2 ml. water, 0.2 ml. serum rinsing the pipette with the water, 0.2 ml. zinc sulfate reagent and 0.2 ml. sodium hydroxide; agitate the tube during the addition of the sodium hydroxide. Stopper, shake vigorously and allow to stand for at least 10 min. Centrifuge at 3000 rpm. for 15 min.

Transfer 0.15 to 0.16 ml. of the filtrates to the microcuvettes for use in the Beckman spectrophotometer model DU (Lowry and Bessey[6]). Read at an optical density of 350 mμ. Treat a water blank in the same way as the filtrates with each set of cuvettes. Add 0.003 ml. 4 N sulfuric acid to each cuvette, stir and make a blank reading. Add 0.006 ml. 0.2% sodium nitrite, stir, allow the color to develop for 10 min. and read. The color begins to fade at about 20 min. so readings must be made promptly.

The transfer of the filtrates is best carried out using Lang-Levy constriction type pipettes (Bessey, Lowry and Brock[7]), to ensure delivery of a constant amount. There is sufficient filtrate to rinse the pipette between deliveries of different samples. "Between-the-lines" pipettes made from 0.25 mm. bore capillary tubing with a drawn-out tip can be used to deliver the sulfuric acid and sodium nitrite. Four divisions on 1 pipette make refilling unnecessary when adding the reagent to the 4 cuvettes. A 2 ml. rubber dropping bulb with a fine glass tip is a simple method of providing an air-stream for stirring.

Find the change in optical density of each cuvette by subtracting the initial from the final reading. Subtract the value for the control serum from those for the samples containing antipyrine. Allow for dilution of the filtrate by multiplying a factor of 4. Make a final correction to bring the value to that of serum water. Serum water: serum water in normal individuals can be assumed to be 0.93 ml./1.00 ml. serum. In this study the serum water was determined for each patient. A sample of serum was weighed in a calibrated and weighed Lang-Levy type constriction pipette. The serum was discharged into a weighed porcelain crucible and the pipette rinsed 3 times with distilled water, the rinsings being added to the crucible. The crucible was placed in an oven at 100 to 110° C. for 24 hr. and, after cooling in a desiccator, was again weighed. The serum water antipyrine was then calculated.

$$\text{Serum water antipyrine} = \text{serum antipyrine} \times \frac{\text{volume of pipette}}{\text{wt. of serum} - \text{wt. of dry serum}}$$

Plot the values for serum water antipyrine against time on semilogarithmic paper, thus defining a straight line, the value at zero time giving the theoretic concentration of antipyrine at the time of injection. Divide this concentration into the amount of antipyrine injected to determine the volume of distribution of antipyrine.

RESULTS

Observations have been made on 24 children and in 20 instances determinations were made by both the deuterium oxide and antipyrine methods. The results are shown in table 1. The children varied in age from birth to 11 years and in weight from 1.93 to 36.65 kg.

Using the values for total body water determined by deuterium oxide dilution as a standard of reference, the antipyrine measured a volume of distribution on an average 1.8% lower with a standard deviation of 4.1%. The exchange of deuterium with hydrogen in organic molecules is believed to account for an estimated volume of distribution which is 1 to 2% higher than the true total body water (Schloerb et al.[8]). Binding of antipyrine by plasma or tissue protein introduces a systematic error into its measurement; the degree of protein binding is not known.

Changes observed in serial determinations of body water should be greater than those which might result from errors in the method if they are to be considered significant. Thus, using antipyrine, in a 4 kg. infant with 3 l. of body water, a change of less than

250 ml. might not be found. In short term studies, a single determination of the total body water, correlated with accurate records of changes in body weight, would be more reliable.

There have been few previous determinations of total body water in children. The

TABLE 2

VALUES FOR TOTAL BODY WATER IN INFANTS OBTAINED BY DESICCATION (FIGURES FROM LITERATURE)

Reference	Age	Body water as per cent body weight
Bischoff[9]	Newborn	66.4
Fehling[10]	Newborn	74
Iob and Swanson[11]	Newborn	79.6
Camerer et al.[12]	Newborn	71.6, 69.2, 73.0, 73.0, 72.0, 72.0

classical studies in the newborn infant made by desiccation are shown in table 2. Deuterium oxide has given values of 73.8, 76.8 and 73.2% body weight in three newborn infants (Flexner et al.[13]).

Values between 70.2 and 83.0% body weight were found in the neonatal period. The premature infants fell into the same range as the full term infants. During the first 6 months of life, there was some decline in body water. Beyond 6 months of age the values varied between 53 and 63% and showed no correlation to age or sex (chart 1 and table 1). The decline in body water expressed as per cent body weight during the first

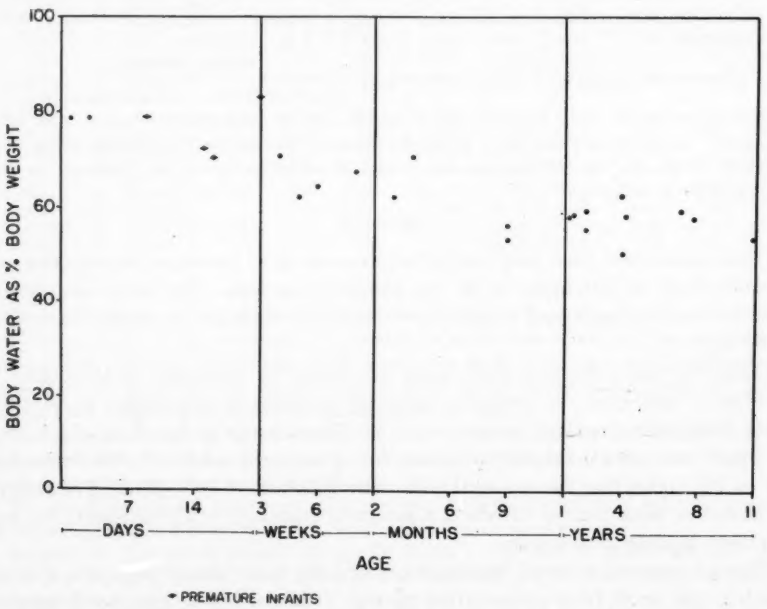

CHART 1. Relationship of total body water expressed as per cent of body weight to age.

6 months of life is consistent with observations (Fellers et al.[14]) on the charges in the volumes of distribution of thiocyanate and sodium[24]. It has been shown[15] that the composition of tissues is much more constant when corrected for their fat content, and it is reasonable to suppose that the changes and variations in body water as per cent body weight are due in large part to differences in body fat content.

Since water makes up the greater part of the body weight, a large absolute loss of water will make but a small percentage change in the water content of the child. For example, a 5 kg. child whose total body water was 80% of the body weight and who

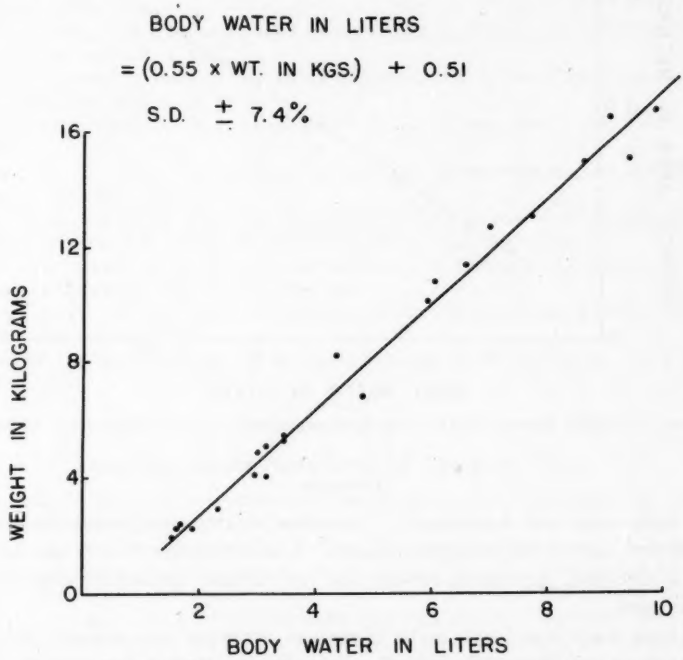

CHART 2. Relation between weight in kilograms and total body water in liters.

then lost 1 l. of water would have a new value of 75% in spite of a loss of one fourth of this body water. It is much better to express the total body water in actual amounts than as a per cent of body weight when considering any particular case.

The actual values of body water expressed as liters show a similar correlation with body weight and surface area (charts 2 and 3). The equations for the best straight lines defining these relationships are shown in the figures, the calculations being made by the method of least squares. The deviation of the data from each line is of the same order. This would be expected, as, in infancy and early childhood, the relationship between body weight and surface area is very nearly linear.[16] The two heaviest children were excluded from these analyses as there were not enough data in that range to draw any conclusion. It is clear that these particular formulae can only be expected to hold for the period studied and allow calculation of total body water only in children up to 20 kg. or 1 sq. m.

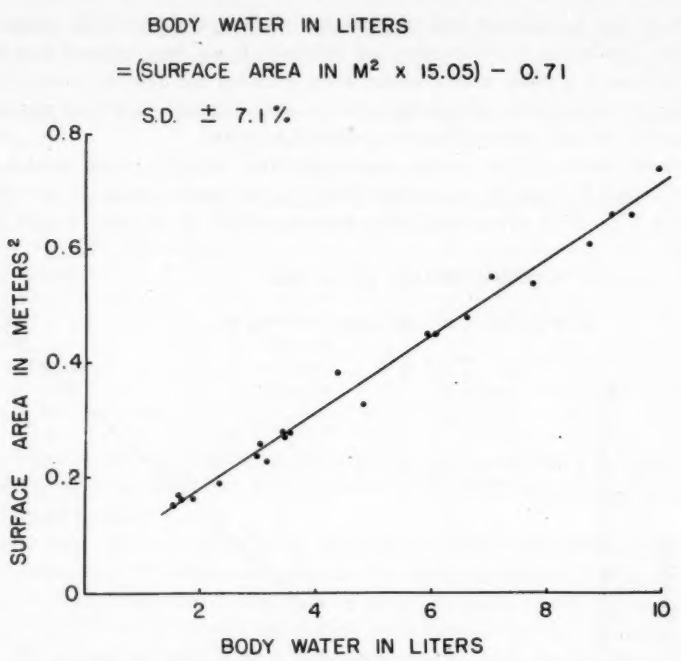

CHART 3. Relation between surface area in square meters and total body water in liters.

SUMMARY

Total body water was determined in 24 normal infants and children by deuterium oxide dilution and by the antipyrine method. A micro-modification of the antipyrine method is described. Agreement between the two methods for determining total body water was good.

Total body water was found to be highest in premature and newborn babies, the values ranging from 70 to 83% of body weight. During the first 6 months of life there was a gradual decrease of body water as per cent body weight. From 6 months to 11 years of age, the values varied between 53 and 63% with no correlation to age or sex.

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REFERENCES

1. Moore, F. D., Determination of total body water and solids with isotopes, Science **104**:157, 1946.
2. Brodie, B. B., Axelrod, J., Soberman, R., and Levy, B. B., Estimation of antipyrine in biological materials, J. Biol. Chem. **179**:25, 1949.
3. Soberman, R., and others, Use of antipyrine in measurement of total body water in man, J. Biol Chem. **179**:31, 1949.

4. Davies, J. A. V., "Rapid" micro-Hinton and capillary Hinton test for syphilis, J. Pediat. **10**:802, 1937.
5. Schloerb, P. R., Friis-Hansen, B. J., Sheldon, D. B., and Moore, F. D., Use of falling drop method to measure deuterium oxide in body fluids, J. Lab. & Clin. Med., to be published.
6. Lowry, O. H., and Bessey, O. A., Adaptation of Beckman spectrophotometer to measurements on minute quantities of biological materials, J. Biol. Chem. **163**:633, 1946.
7. Bessey, O. A., Lowry, O. H., and Brock, M. J., Method for rapid determination of alkaline phosphatase with five cubic millimeters of serum, J. Biol. Chem. **164**:321, 1946.
8. Schloerb, P. R., and others, Measurement of total body water in human subject by deuterium oxide dilution, with consideration of dynamics of deuterium distribution, J. Clin. Investigation **29**:1296, 1950.
9. Bischoff, E., Einige Gewichts und Trocken-Bestimmungen der Organe des menschlichen Korpers, Ztschr. f. rat. Med. **20**:75, 1863.
10. Fehling, H., quoted by Shohl, A. T., Mineral Metabolism, ed. 1, New York, Reinhold Publishing Corporation, 1939, p. 15.
11. Iob, V., and Swanson, W. W., Mineral growth in human fetus, Am. J. Dis. Child. **47**:302, 1934.
12. Camerer, W., Jr., Söldner and Herzog, Die chemische Zusammensetzung des Neugeborenen, Ztschr. f. Biol. **43**:1, 1902.
13. Flexner, L. B., and others, Estimation of extracellular and total body water in newborn human infant with radioactive sodium and deuterium oxide, J. Pediat. **30**:413, 1947.
14. Fellers, F. X., Barnett, H. L., Hare, K., and McNamara, H., Change in thiocyanate and sodium^{24} spaces during growth, PEDIATRICS **3**:622, 1949.
15. Hastings, A. B., and Eichelberger, L., Exchange of salt and water between muscle and blood, J. Biol. Chem. **117**:73, 1937.
16. Du Bois, E. F., Basal Metabolism in Health and Disease, ed. 2, Philadelphia, Lea & Febiger, 1927, p. 124.

SPANISH ABSTRACT

Determinación del Agua Total del Cuerpo en Niños

El agua total del cuerpo fué determinada mediante los metodos del "deuterium oxide" y la dilución simultanea de antipirina, en 24 niños normales. En éste estudio se observó una correlación adecuada entre los dos metodos. Los autores describen una micro-modificación del metodo de la antipirina. Se encontró que los valores mas altos del agua total del cuerpo (de un 70 a 80% del peso del cuerpo) ocurrieron en prematuros y niños recién nacidos. Estos valores decrecieron gradualmente durante los seís primeros meses de la vida, y entre los seis meses y los once años de edad oscilaron entre un 53% a un 63% del peso del cuerpo. Los autores indican que en la comparación de los cambios del agua del cuerpo de un caso en particular, la determinación actual de la cantidad de agua del cuerpo es una forma mas satisfactoria de expresión que mediante el uso de porcientos por peso del cuerpo. Esto es debido al hecho de que cambios significantes en las cantidades absolutas del agua del cuerpo, solo reflejan pequeños cambios en terminos de concentración de agua del cuerpo.

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EFFECT OF DEHYDRATION PRODUCED BY WATER DEPRIVATION, DIARRHEA AND VOMITING ON RENAL FUNCTION IN INFANTS

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ALTERATIONS occurring in renal function during dehydration in infants deprived of water and during diarrheal disease and vomiting have not been defined clearly. Young and McCance[1] studied seven infants with diarrhea and found that the rate of glomerular filtration was lower than adult values. From the data presented by them it is not possible to compare the values of their sick infants with the low values found in normal infants.[2–4] They do not report values for glomerular filtration during recovery; it is, therefore, not possible to estimate the degree of depression in glomerular filtration which occurred during dehydration in their patients. In a study on water deprivation in four adults, in whom there was a 4 to 7% weight loss, Black, McCance and Young[5] found what they believed to be insignificant reductions in the glomerular filtration rate. Barnett et al.[6] conclude that with "moderate" water deprivation (food was also withdrawn) in premature infants there is no diminution in glomerular filtration rate.

The experiments recorded in this report were designed to show the changes in renal mechanisms brought about when dehydration was induced by water deprivation to the magnitude seen in disease in infancy. These changes are compared to the alterations in renal function occurring in diarrheal disease and vomiting in the same age group.

METHODS

The effects of dehydration in these 3 conditions were studied in 19 infants. Seven infants were deprived of water for 4 to 5 days, resulting in 3 to 10% loss of body weight. Daily intake of water varied from 20 to 45 cc./kg./day. Caloric intake was reduced to about half the control intake in 3 infants during the dehydration period. In the remaining 4 infants the caloric intake remained approximately at the predehydration level. Nine infants studied were admitted to the Children's Hospital of Buffalo with diarrhea and 3 others were infants vomiting with high intestinal obstruction (2 with pyloric stenosis, 1 with duodenal obstruction). The initial study of renal function was made shortly after hospital admission and subsequent observations were repeated after recovery.

Inulin clearances by the single injection technic and endogenous creatinine clearances were used as measures of glomerular filtration rates. Clearances of para-aminohippurate were determined according to the method of Goldring and Chasis.[7] Inulin was given as a single injection intravenously except in 1 case when it was given subcutaneously. Para-aminohippuric acid was given subcutaneously also as a single injection in Cases 2 and 4 and as a continuous intravenous infusion in Case 16. The amount of inulin and para-aminohippurate was calculated on the basis of weight, age and degree of dehydration, in order to obtain a concentration of 50 mg./100 cc. of blood for inulin and 2 mg./100 cc. for para-aminohippurate.

The urine was collected by catheter draining into a 25 ml. volumetric flask, and the bladder was completely emptied by air instillations. It was then diluted to volume with distilled water from a burette and the urine volume calculated by difference. Serum carbon dioxide content was estimated

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by the method of Van Slyke,[8] chloride by the method of Sendroy as modified by Van Slyke and Hiller,[9] urea by the micro-diffusion method of Conway[10] and creatinine by the method of Hare and Hare.[11] All sodium and potassium determinations were made using a Perkin-Elmer Flame Photometer, Model 52A, with lithium nitrate as internal standard. Inulin was determined by the method of Hubbard and Loomis,[12] using the acid mixture for hydrolysis of inulin as modified by Harrison[13] and para-aminohippurate as described by Goldring and Chasis.[7]

All determinations were done in duplicate. When colorimetric methods were used, standard solutions were analyzed in order to construct a calibration curve for each set of unknown solutions. Samples of plasma and urine prior to injection of inulin and para-aminohippurate were used for blank determinations in all clearances. No correction was made for the delay in passage of the urine from renal parenchyma to catheter. In the tables absolute values are presented and no correction for surface area is made.

Results

Water Deprivation: Table 1 presents the pertinent data obtained from seven patients all of whom were deprived of water for 4 to 5 days. Caloric intake of food was maintained by giving the infants concentrated formulas of powdered milk. Four of these infants were mongolian idiots, two were mentally deficient and one was normal.* In none was there any history or laboratory evidence of previous renal disease. Losses in body weight from 3.6 to 9.4% were accompanied by a reduction of 36 to 66% in the glomerular filtration rates. Urea clearances followed the same pattern as did the inulin clearances, but in each instance the fall (ranging between 57 to 81% of the original values) was greater than the inulin clearance fall. Para-aminohippurate was measured in Cases 2 and 4 and in both infants dehydration resulted in lower clearances of this substance.

During dehydration the blood urea nitrogen was elevated significantly in Cases 1, 2, 3 and 4. In Cases 5, 6 and 7, where the caloric intake was reduced, significant elevations of the blood urea nitrogen did not occur despite the fact that in these infants the glomerular filtration rate fell. In each instance there was a marked increase in serum sodium and chloride values leading to plasma hyperosmolarity. Extremely low urine flows were obtained during the dehydration periods. The U/P ratios for inulin were greatly elevated over control values in all cases except Case 4 in which it was only slightly elevated.

Table 2 shows the data obtained from 12 patients with dehydration secondary to disease. Nine were children with diarrheal disease, two suffered from vomiting due to

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* Since most of the patients used in the water deprivation study were mongolian idiots or otherwise mentally defective children, one could not with certainty be assured that their kidney function was comparable to normal infants in the same age group. Roosen-Runge,[14] in a study of renal anatomy in children with varying types of congenital cerebral defects and cerebral birth trauma, found in general the kidneys to be small with retardation in differentiation and growth of glomeruli and tubules. He noted that the retardation process was most conspicuous in children over 1 year of age. Mongolian infants were not included in his study. Benda,[15] however, noted that the kidneys of mongolian idiots are small and underweight with retardation in development of glomeruli. Again, he also finds that this retardation is more apparent in children over 5 years of age. It should be pointed out that the infants in the present study were all under 2 years of age, most of them under 4 months. Vesterdal and Tudvad,[16] in a study of the glomerular filtration rate and renal plasma flow in infants in the 1st 3 mo. of life, found that the 2 mongolian infants in their group had clearances comparable to the normal. The present investigators believe that the use of these mentally defective children in this study does not disturb the conclusions drawn. Case 7, a normal infant, responded to dehydration as did the others.

TABLE 1

Data on Infants Dehydrated by Water Deprivation

Patient Age Diagnosis	Wt. Kg.	% Loss	Date	Intake/kg./day Fluid ml.	Cal.	Plasma or Serum B.U.N. mg. %	T.P. gm. %	CO_2 mEq./l.	Cl mEq./l.	Na mEq./l.	K mEq./l.	HCT	Renal Function U.F. ml./min.	Glom. Filt. ml./min. C_I	C_{cr}	C_{PAH} ml./min.	C_{Urea} ml./min.	$\frac{U}{P}$	Surface Area M^2
Case 1 C. I. 21 days Mongolism	3.10	Control	12-7	90	140		4.4	19.5				32	.236 .225	5.10 5.40				22 24	0.215
	3.37	5%	12-31	30	65	35	6.5	25.8		172		33	.024 .031	3.54 3.45				147 110	0.231
	3.75	Control	1-9	200	100		6.1			155		25	.25 .37 .45	6.75 5.43 5.94				27 22 13	0.249
Case 2 G. E. 11 days Mongolism Premature	2.21	Adm.	12-6			15				150	5.4		.033 .022 .026	2.80 2.30 1.67	2.07 1.29 2.04		0.71 0.47 0.66	85 104 64	0.174
	2.04	7.7%	12-10	30	80	41	5.8	29	130	172	4.9	50	.012 .011 .005	0.99 0.92 0.65	0.664 0.600 0.396	2.53 2.98 2.48	0.16 0.13 0.07	80 84 130	0.166
	2.59	Control	12-22	180	100	24	6.2	24	114	148	5.9		.036 .051 .048 .036	2.05 2.12 2.46 2.37	1.74 2.36 2.13 1.97	10.6 11.0 9.1	0.65 0.64 0.59 0.65	55 41 50 64	0.194
Case 3 L. A. C. 5 mo. Mongolism	5.20	Control	9-2	180	100		6.6		107	142	6.00		.22 .37 .21		10.0 10.2 9.25			45 27 44	0.302
	4.40	9.4%	9-8	20	100	51.8	8.2		134	176	7.15	37	.05 .05 .06 .04 .05 .04	 5.00 4.60 3.10	3.46 3.26 4.13 3.39 4.04 2.58		1.93 1.72 1.67	 124 118 74	0.262

TABLE 1—(*continued*)

Patient Age Diagnosis	Wt. Kg.	Wt. % Loss	Date	Intake/kg./day Fluid ml.	Intake/kg./day Cal.	Plasma or Serum B.U.N. mg. %	Plasma or Serum T.P. gm. %	Plasma or Serum CO_2 mEq./l.	Plasma or Serum Cl mEq./l.	Plasma or Serum Na mEq./l.	Plasma or Serum K mEq./l.	HCT	Renal Function U.F. ml./min.	Glom. Filt. ml./min. C_I	Glom. Filt. ml./min. C_{cr}	C_{PAH} ml./min.	C_{Urea} ml./min.	$\frac{U^*}{P_i}$	Surface Area M^2
	5.58	Control	9-19	180	100	35			106	144	6.10	34	.44 .26 .39 .41		12.1 10.8 10.0 14.2		3.57 3.96 4.36	28 41 26 34	0.317
Case 4 B. D. 21 days Mongolism	2.36	6.7%	3-4	34	130	60	6.7		124	168		64	.04 .03	2.00 1.73		5.17 4.45		50 54	0.182
	2.61	Control	3-16	180	100	29	8.1		98	144		39	.14 .11	3.00 3.10		16.2 14.4		21 28	0.195
Case 5 E. C. 14 mo. Mental Retardation	6.30	3.6%	3-18	46	55	27	8.54		117	171		33	.052 .060	7.70 9.70			2.6	149 161	0.349
	6.70	Control	3-23	180	120	22	5.40		106	140		32	.18 .18	16.00 16.00			10.8 10.6	86 86	0.377
Case 6 R. P. 14 mo. Mental Retardation	10.70	6.4%	2-24	27	53	16	7.2		116	179		39	.08 .06	9.8 8.2			3.9 3.1	122 137	0.514
	11.20	Control	3-9	180	100	15	7.5		101	143		41	.44 .35	27.0 24.0			16.4 15.0	61 69	0.530
Case 7 R. L. 4 mo. No Disease	5.74	8.1%	4-12	20	60	18		21.6	115 420 ml.	Water	Orally		.025 .025 - - - - .078 .10	6.70 8.90 - - - - 19.6 21.0	5.22 7.60 - - - - 15.8 15.2			208 306 25 21	0.322

* U/P ratios calculated from the inulin clearances except in Case 7 where creatinine clearance was used for the calculation.

TABLE 2

DATA ON INFANTS DEHYDRATED BY VOMITING AND DIARRHEAL DISEASE

Patient Age Diagnosis	Wt. kg.	Date	Clinical Remarks	Plasma or Serum							HCT	Renal Function						Surface Area M^2
				B.U.N. mg. %	T.P. gm. %	CO_2 mEq./l.	Cl mEq./l.	Na mEq./l.	K mEq./l.	pH		U.F. ml./min.	Glom. Filt. ml./min. C_I	Glom. Filt. ml./min. C_{cr}	C_{PAH} ml./min.	C_{Ures} ml./min.	$\frac{U}{P}$	
Case 8 M. R. 14 days Duodenal Obstruction	2.78	9-30	Moderate	48.4	6.83	35	83	144	4.37	7.46	51	.009 .007		0.87 0.50		.05 .045	94 73	0.204
		10-1	i.v. Fluid	40.0	5.54	28.6	95	128	3.7			.10 .12		2.02 2.24		.44 .54	20 18	
	2.84	10-11	Recovery	16.2	6.4	20.4	101	148	6.3			.07 .09		5.22 6.04		1.71 2.53	75 61	0.207
Case 9 J. J. 30 days Pyloric Stenosis	3.00	10-25	Severe	19.9	6.7	42.5	81	134	5.3			.021 .007		2.40 1.55		.59 .38	114 220	0.214
		10-26	i.v. Fluid	10.6		32.8	95	146	4.4			.092		3.60		3.15	38	
	3.40	11-4	Recovery	20		22.2	108	142	5.9			.14 .17		12.10 10.70		5.60 4.82	84 60	0.233
Case 10 K. W. 3 mo. Pyloric Stenosis	3.16	10-25	Severe	15.4		41.3	70	126	4.0	7.37		.02 .03		3.47 5.40		.44 .80	157 155	0.222
		10-26	i.v. Fluid	12.8		24.6	88	128	3.1			.24		6.30		2.22	26	
	3.30	11-4	Recovery	15.0		18.7	111	134	4.7			.05 .04		7.10 6.00		2.64 2.00	140 140	0.228
Case 11 W. T. 2 mo. Diarrhea	5.10	10-19	Severe	42.8	6.8	8.9	133	140	3.6		30	.06		5.0		1.62	77	0.292
	5.00	10-29	Recovery	5.1	7.7		112	150	5.6			.35 .17		12.0 9.2		4.45 2.85	34 52	0.292
Case 12 M. B. 16 days Diarrhea	2.98	10-19	Mild	39.6	5.5	17.6	108	124	4.5		40	.16 .31		4.97 4.35		4.32 4.17	31 14	0.213
	3.10	10-29	Recovery	15.0		17.4	112	146	6.0			.61 .51		4.35 4.45		2.04 1.77	7.1 8.9	0.219
Case 13 C. S. 12 days Diarrhea	2.18	10-11	i.v. Fluid	73			127	151	4.1			.042 .034 .054		2.38 2.05 2.58		.443 .303 .540	56 61 49	0.173
	2.73	10-21	Recovery	33			105	145	4.8			.07 .12 .09		4.45 5.52 4.74		1.52 2.90 1.93	66 45 53	0.201

TABLE 2—(*continued*)

Patient Age Diagnosis	Wt. kg.	Date	Clinical Remarks	Plasma or Serum							HCT	Renal Function						Surface Area M^2
				B.U.N. mg. %	T.P. gm. %	CO_2 mEq./l.	Cl mEq./l.	Na mEq./l.	K mEq./l.	pH		U.F. ml./min.	Glom. Filt. ml./min. C_I	Glom. Filt. ml./min. C_{cr}	C_{PAH} ml./min.	C_{Urea} ml./min.	U* / P	
Case 14 C. C. 8 mo. Diarrhea	7.30	9-27	i.v. Fluid	49	9.9	13.1	100	131	7.1	7.34		.49		11.0		5.90	43	0.399
	7.60	9-30	Recovery	16		21.6	102	141	4.7			.27 .26		13.0 15.0		4.32 3.84	48 58	0.409
Case 15 L. S. 11 mo. Diarrhea	6.70	9-27	Died	32	6.2	12.4	126	138	2.6	6.91		.35 .43 .44		18.0 18.0 17.0		10.0 11.0 11.0	51 42 37	0.366
Case 16 W. D. 20 mo. Diarrhea Shock	8.20	12-10	Shock i.v. Fluid	88	7.2	16.7	98			6.9	35	.068 .122 .125	0.39 0.60 1.00		3.96 2.53 4.21		5.8 4.9 8.0	0.430
	8.40	12-15	Improved	26							31	.24 .16 .20	9.00 10.20 9.70		24.0 22.6 25.8		38 64 48	0.438
	8.40	12-23	Recovery	27	6.8		108			7.34	29	.67 .63	18.0 18.2		190 155		27 29	0.438
Case 17 R. S. 8 mo. Diarrhea Malnutrition	4.70	12-23	i.v. Fluid	35		23.8	120					.049 .05		1.89 2.30			38 46	0.289
	4.65	1-6	Recovery	26		20.0						.13 .15 .16	8.70 8.60 9.30				67 57 58	0.287
Case 18 K. B. 7 mo. Diarrhea	8.62	1-7	i.v. Fluid	34	9.8	12.8	129	162				.059 .049 .127		5.10 6.51 6.50		2.79 3.54 3.70	86 134 137	0.446
	9.50	1-8	Improved	14	5.0		128				29	.267 .139	13.7 10.7	9.42 9.58			51 77	0.475
Case 19 L. M. Diarrhea Newborn	2.70	2-11	Shock i.v. Fluid	101	8.3	14.8	137	176				.04 .023		.14 .10			3.5 4.3	0.200
	2.73	2-12	Improved	39.8	6.8	14.6	117					.057 .045		2.16 1.93		1.27 .90	38 43	0.201

* U/P ratios calculated from creatinine clearances except in Cases 16, 17 and 18 where the inulin clearances were used.

hypertrophic pyloric stenosis and one from duodenal obstruction. In all, 62 individual periods were studied. The first clearance periods were made immediately on admission to the hospital. In the very sick infants fluid therapy was begun while the clearance test was underway; therefore, the clearances recorded are probably higher than existed in the pretreatment phase.

The second series of clearance studies were made just before the patients were discharged from the hospital. In the very sick infants endogenous creatinine clearance alone was used as the measure of glomerular filtration.

Pyloric stenosis (one of the cases included in this group had a duodenal obstruction): In the 3 cases recorded, the glomerular filtration rate was 12%, 17% and 68% of that found during the recovery phase. In a fourth case not listed, the value during dehydration was 13% of the recovery value. Burnett, Burrows and Commons[17] found a reduction in glomerular filtration rate with alkalosis associated with pyloric obstruction in adults. Whether alkalosis in the patients in the present study was an added factor in producing the reduced glomerular filtration rate cannot be stated. As in the case of experimental water deprivation, the urea clearance in these patients was reduced during the dehydration state to a greater degree than was the glomerular filtration rate. In Case 8 it fell to 5.7% of the glomerular filtration rate. The creatinine U/P ratios were all high during dehydration. In two of the three cases with remarkable reduction in glomerular filtration rate, the blood urea nitrogen values were not elevated, probably a result of starvation. Alkalosis was present in each case with a concomitant reduction in serum chloride values. It is interesting that there was a fall from normal serum K levels during the intravenous administration of fluids.

Diarrhea: Each of these infants was severely dehydrated with the exception of Case 12. It was not possible to measure the degree of dehydration accurately, as the weight change did not solely measure water loss. In all cases except Case 12, a mildly dehydrated infant, the glomerular filtration rate was significantly lowered. In the two children on whom the test was performed during "shock" the glomerular filtration rates were almost at the vanishing point. In Case 16 where shock existed the para-aminohippurate clearance was practically zero. In several of the patients in this diarrhea group the degree of reduction in urea clearance when compared to the reduction in glomerular filtration rate was not as great as was found in the other two groups. It must be pointed out that the first clearance test was usually made after therapy was begun, which may have influenced the ratio of urea clearance to glomerular filtration rate. The blood urea nitrogen values represent levels determined before fluid was given. There was a variable pattern of serum sodium, potassium and chloride. In two infants in shock, creatinine U/P ratios calculated before therapy was begun do not show the high values seen in water deprivation and pyloric stenosis even though glomerular filtration rates were severely reduced.

Discussion

It is assumed that in these states of marked dehydration, inulin and endogenous creatinine clearances still are a valid measure of glomerular filtration rate. Obviously, one might expect greater errors in total urine collections at very low urine flows than when there is a large volume of urine. In these studies the periods of collections were prolonged for this reason. The fact that the separate periods during dehydration show a close correlation in glomerular filtration rates would indicate satisfactory urine collections.

The validity of the use of a single injection of inulin in determining glomerular filtration is dependent upon the rate of fall of plasma inulin concentration. Chart 1 shows the changes in plasma inulin concentration following a single intravenous injection of inulin and in two instances following a subcutaneous injection. The slopes in those cases with single intravenous injections are relatively flat and tend to minimize arteriovenous differences. The error in clearances based upon venous blood[18] becomes, therefore, insignificant in these data. In the two cases where inulin was given subcutaneously with rising inulin blood concentrations, there were also reduced glomerular filtration rates during dehydration. In dehydration with very small urine flows the error in calculating the rate of urine flow from renal tubule to bladder is greater than under normal circumstances because of the relatively larger dead space in pelves and ureters and the

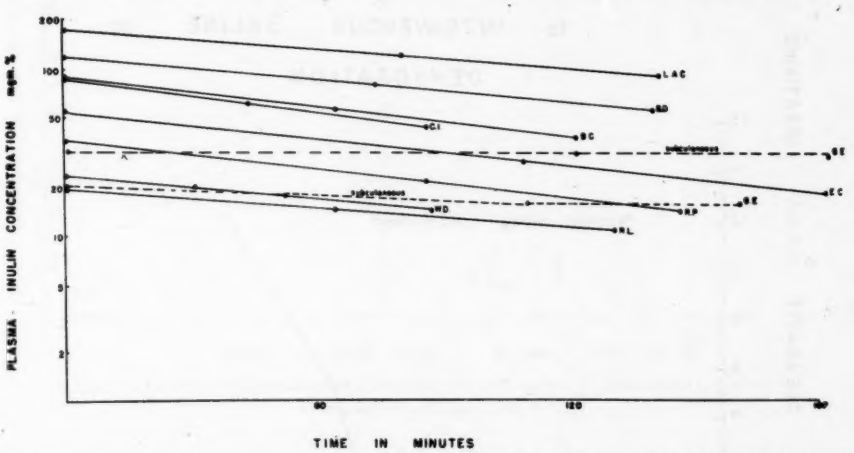

CHART 1. Slopes of plasma inulin concentrations following single intravenous injection. Rising slopes follow subcutaneous injections. In all instances, first plasma determination was made after equilibration period of 90 min.

greater delay time with low urine flows. The estimated concentration of plasma inulin at the midpoints of the periods during dehydration are really not true midpoints but are shifted toward the right. Actually, then the true glomerular filtration rates during dehydration are most probably lower than the figures given. This latter fact may possibly account for the high inulin/creatinine ratios obtained in the dehydrated child, since creatinine blood levels are constant under these conditions.

In infants, dehydration brought about by water deprivation, diarrhea and vomiting results in a significant fall in the glomerular filtration rate which returns to normal values with hydration. Kenney,[19] in a study of three adults, also found a reduction in glomerular filtration rate with water deprivation. A reasonable explanation for the difference in the data presented here and that of Barnett et al.[6] in water deprivation is that in the subjects studied here a greater degree of dehydration was obtained than in their premature infants. Whereas, Black et al.,[5] in their studies, conclude that there were only insignificant reductions in glomerular filtration rate with dehydration, actually their data indicate a reduction of 11.6 to 23%, which might have been greater had their subjects been further

dehydrated. The relatively small extracellular water reserve in the infant may account for a more advanced alteration in kidney function during comparable dehydration. In the infants reported here the water intake was reduced to 20 to 46 cc./kg. body weight/day. In earlier trial periods levels of water intake much above this amount did not result in significant reduction in the glomerular filtration rate. The two infants, numbers 16 and 19, who were in a state of shock during dehydration had extremely low glomerular filtration rates. In the two instances where para-aminohippurate clearances (as a measure of renal plasma flow) were simultaneously performed, they were also reduced, suggesting that the fall in glomerular filtration rate was related to the reduced renal

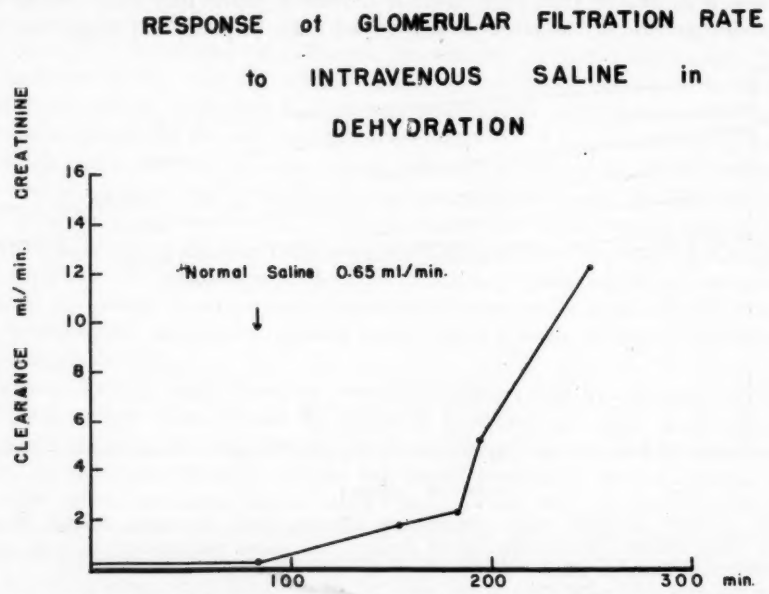

CHART 2. Effect of fluid therapy on glomerular filtration in recovery from dehydration in child with pyloric stenosis. Fluid therapy was continuous from point noted by arrow until end of experiment.

circulation. Two patients studied after this report was completed showed a similar response in both glomerular filtration rate and para-aminohippurate clearances. Lauson et al.[20] found a reduction in both renal blood flow and glomerular filtration rate during "shock" states in adults. The filtration fraction in their patients showed wide variation; many were considerably reduced and a few were high. Handley, Sigafoos and LaForge[21] also found a reduction in glomerular filtration rate and renal plasma flow in dogs dehydrated by diuretics. These latter authors found an associated fall in Tm glucose and Tm para-aminohippurate. The filtration fraction in the dog was unaltered in dehydration suggesting that the reduced glomerular filtration rate may be dependent upon a reduced renal plasma flow.

Chart 2 shows the rapid rise in glomerular filtration rate following recovery from dehydration in an infant with pyloric stenosis receiving an intravenous infusion of normal saline. Within one hour after the infusion was begun, the glomerular filtration

rate rose and in about 2½ hours it had risen to above the normal average values for a child of this age.[2] In the water deprivation group it is apparent that recovery is rapid with hydration. In Case 7 the oral administration of 420 cc. of water raised the filtration rate within an hour from a previous low of one-third normal to normal values. In the pyloric stenosis group recovery was complete within 11 days. (These rates may have returned to normal earlier, the tests were not repeated prior to this time.) In the diarrhea group recovery had generally occurred by the end of 10 days. In a single case a second test performed after three days of therapy still showed a reduced glomerular filtration

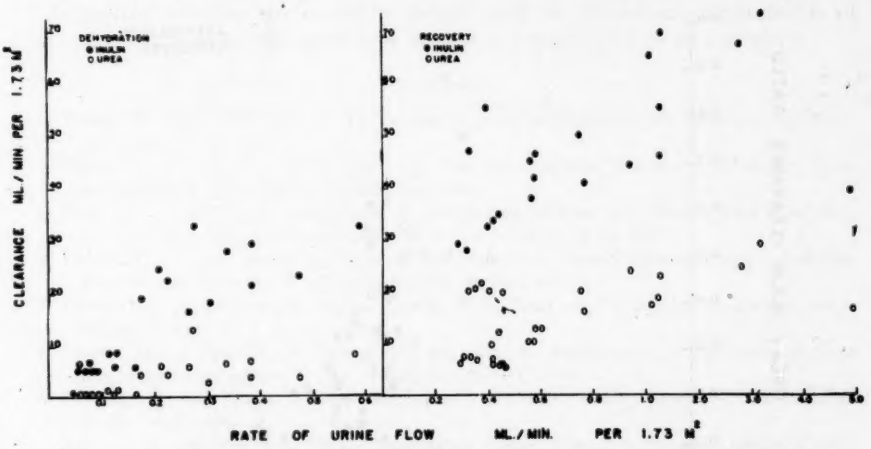

CHART 3. Correlation between urine flow (indication of degree of dehydration), glomerular filtration rate and urea clearance.

rate (Case 14); one case in "shock" (Case 16) had recovered when a second test was performed 13 days after treatment was instituted.

Chart 3 shows the relationship of glomerular filtration rate to urine flow, where the urine flow values are corrected to the adult surface area of 1.73 sq. m. and are an expression of the degree of dehydration. With slight reductions in the urine flow there is no appreciable change in glomerular filtration rate. The fall in glomerular filtration rate is significant at 0.4 cc./min. and a critical drop is seen at 0.2 cc./min. Lauson, Bradley and Cournand[20] found that in adults with shock there was a similar correlation between urine flow and the glomerular filtration rate. The failure of others to find this association[5] is due to the fact that sufficiently low urine flows were not obtained in their studies. The fall in urea clearance with maintained glomerular filtration rates, as noted by many others, occurs at much higher urine flows. The fall in urea clearance at a time when the glomerular filtration rate is maintained at normal levels and the urine flow is reduced would indicate increased tubular reabsorption of urea and water. Since these are the findings in mild dehydration, it is believed that the mechanism for water conservation in these mild states is largely by tubular reabsorption. In states of severe dehydration produced by experimental water deprivation, diarrhea, and vomiting of pyloric stenosis, the fall in glomerular filtration rate also plays a part in the diminution of water excretion actually enhancing the tubular mechanism by delivering small quantities for tubular re-

absorption. This is manifest in those cases where the urea clearance has dropped to a greater degree than the inulin and creatinine clearances.

Chart 4 shows the relationship of the rate of reabsorption of urea to the concentration of the glomerular filtrate (water reabsorption) in infants during dehydration and recovery. It will be noted that an inverse relationship exists between the U/P ratio of inulin and the urea/inulin clearance ratio. This relationship with the wide scatter of the data is similar to that found in the premature infant[6] and closely parallels that found in glomerulonephritis by Chasis and Smith.[22] The three top circles on the graph represent

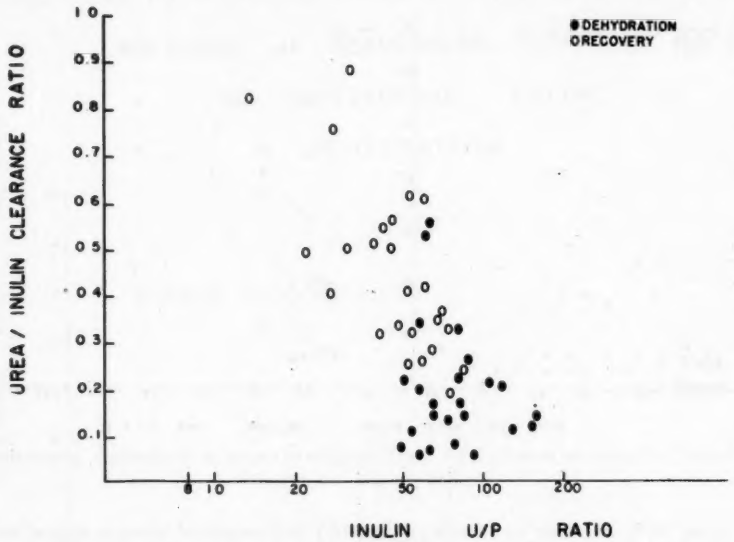

CHART 4. Relationship between tubular reabsorption of water (inulin U/P ratio) and reabsorption of urea.

a single case of newborn infant with high urine flow. Here urea clearance closely approximates inulin clearance.

In two infants studied during shock in diarrhea, the U/P ratios were not as high as might be expected with the very low urine flow, suggesting that disturbed tubular water reabsorption existed. Selkurt[23] found that anoxia produced a similar effect on the U/P ratio in dogs and Lauson et al.[20] found that in adults in shock when the glomerular filtration rate was very low (less than 20 cc./min.) the U/P ratio was low, indicating loss of concentrating capacity of the tubules (water reabsorption). This is in accord with the observation that the specific gravity of the urine in shock tends to become fixed at about 1.013.[24] Dubs,[25] in a study of the urine concentrating capacity in small infants, found that infants with diarrhea and dehydration had in most instances a lower osmolarity of their urine when compared to normal infants dehydrated by water deprivation. The changes in excretion of electrolytes during dehydration will be presented by the authors in a subsequent paper.

Summary and Conclusions

Dehydration when of sufficient severity depresses the glomerular filtration rate significantly. The high inulin and creatinine U/P ratios during dehydration indicate water conservation by the tubules. Depressed glomerular filtration rates may enhance this mechanism.

The tendency to the lower than expected rise in U/P ratio with low urine flows during dehydration in diarrheal disease suggests disturbed tubular mechanism for water reabsorption.

Glomerular filtration rate is rapidly restored with the intravenous administration of fluid. Restoration to normal values may proceed at a slower pace in the sick infant.

References

1. Young, W. F., and McCance, R. A., Secretion of urine by dehydrated and normal infants, Arch. Dis. Child. **17**:65, 1942.
2. Rubin, M. I., Bruck, E., and Rapoport, M., Maturation of renal function in childhood: Clearance studies, J. Clin. Investigation **28**:1144, 1949.
3. West, J. R., Smith, H. W., and Chasis, H., Glomerular filtration rate, effective renal blood flow, and maximal tubular excretory capacity in infancy, J. Pediat. **32**:10, 1948.
4. Barnett, H. L., Renal physiology in infants and children. I. Method for estimation of glomerular filtration rate, Proc. Soc. Exper. Biol. & Med. **44**:654, 1940.
5. Black, D. A. K., McCance, R. A., and Young, W. F., Function of kidney in dehydration, Nature **150**:461, 1942.
6. Barnett, H. L., Hare, K., McNamara, H., and Hare, R., Measurement of glomerular filtration rate in premature infants, J. Clin. Investigation **27**:691, 1948.
7. Goldring, W., and Chasis, H., Hypertension and hypertensive disease, New York, The Commonwealth Fund, 1944.
8. Peters, J. P., and Van Slyke, D. D., Quantitative Clinical Chemistry: Methods, Baltimore, Williams & Wilkins Company, 1932, vol. 2.
9. Hawk, P. S., and Bergeim, O., Practical Physiological Chemistry, ed. 12, Philadelphia, P. Blakiston's Son & Company, Inc., 1937.
10. Conway, E. J., Micro-Diffusion Analysis and Volumetric Error, New York, D. Van Nostrand Company, Inc., 1940.
11. Hare, R. S., and Hare, K., Determination of creatinine in blood and urine, Federation Proc. **8**:68, 1949.
12. Hubbard, R. S., and Loomis, T. A., Determination of inulin, J. Biol. Chem. **145**:641, 1942.
13. Harrison, H. E., Modification of diphenylamine method for determination of inulin, Proc. Soc. Exper. Biol. & Med. **49**:111, 1942.
14. Roosen-Runge, E. C., Retardation of postnatal development of kidneys in persons with early cerebral lesions, Am. J. Dis. Child. **77**:185, 1949.
15. Benda, C. E., Mongolism and Cretinism, New York, Grune & Stratton, 1946.
16. Vesterdal, J., and Tudvad, F., Studies on kidney function in premature and full-term infants by estimation of inulin and para-aminohippurate clearances, Acta pediat. **37**:429, 1949.
17. Burnett, C. H., Burrows, B. A., and Commons, R. R., Studies of alkalosis. I. Renal function during and following alkalosis resulting from pyloric obstruction, J. Clin. Investigation **29**:169, 1950.
18. Tacket, H. S., and Houck, C. R., Measurement of renal hemodynamics in man by "slope method" without urinalysis, Proc. Soc. Exper. Biol. & Med. **74**:317, 1950.
19. Kenney, R. A., Effects of water deprivation on renal hemodynamics in man, Acta med. Scandinav. **135**:172, 1949.
20. Lauson, H. D., Bradley, S. E., and Cournand, A., Renal circulation in shock, J. Clin. Investigation **23**:381, 1944.
21. Handley, C. A., Sigafoos, R. B., and LaForge, M., Proportional changes in renal tubular reabsorp-

tion of dextrose and excretion of para-aminohippurate with changes in glomerular filtration, Am. J. Physiol. **159**:160, 1949.
22. Chasis, H., and Smith, H. W., Excretion of urea in normal man and in subjects with glomerulonephritis, J. Clin. Investigation **17**:347, 1938.
23. Selkurt, E. E., Changes in renal clearance following complete ischemia of kidney, Am. J. Physiol. **144**:395, 1945.
24. Fishberg, A. M., Heart Failure, Philadelphia, Lea & Febiger, 1937, p. 581.
25. Dubs, E. J., Studies of urine osmolarity in infant, presented before the Society for Pediatric Research, May 4, 1948.

SPANISH ABSTRACT

Efectos de la Deshidratación Producida por Deprivación de Agua, Diarrea y Vomitos, en la Función Renal de Infantes

Los autores estudiaron los efectos de la deshidratación producida por la deprivación de agua, diarrea y vomitos sobre la función renal de un total de 19 infantes.

El volumen de filtración glomerular fué estimado mediante la excreción de inulina y creatinina endogena, el "renal plasma flow" mediante la prueba excretoria con para-aminohippurate, y la reabsorcion tubular del agua mediante la determinacion de los cocientes de inulina y creatinina (U/P ratios). El volumen de filtracion glomerular disminuyó notablemente cuando la deshidratación producida por estas tres causas fué de intensidad suficiente. El aumento de los A/P ratios encontrados durante la deshidratación, es una indicación de la conservación del agua mediante la reabsorción tubular. En las diarreas se observó que los A/P ratios no aumentararon a los valores anticipados, lo que sugiere una depresion de la funcion tubular. El volumen de filtración glomerular es rapidamente restablecido con la administracion intravenosa de fluido. Los cambios en la excreción de electrolitos ocurridos durante la deshidratacion seran presentados en el proximo trabajo.

219 Bryant Street

OBSERVATIONS ON 26 INFANTS UNDER ONE YEAR OF AGE OPERATED ON FOR TETRALOGY OF FALLOT OR TRICUSPID ATRESIA

By C. R. LEININGER, M.D., AND STANLEY GIBSON, M.D.
San Rafael, Calif., and Chicago

FIVE years have elapsed since Blalock and Taussig[1] first reported a surgical technic for relieving congenital pulmonary stenosis. Four years ago the Potts-Smith modification of this technic[2] was instituted at Children's Memorial Hospital, and during this period, Potts and his associates have created an anastomosis in 234 instances. The over-all mortality was 9.8%. The mortality in the age group of 3 to 16 years was only 2.9%. Yet in the group below the age of 1 year, the mortality was 33.3%. It is this group which is considered in this paper.

The preoperative diagnosis was tetralogy of Fallot in 19 cases and tricuspid atresia in seven cases. A Potts-Smith procedure was performed in 22 patients. The side of the aortic arch was misdiagnosed in one child. Fortunately, the left subclavian artery was sufficiently large in this case so that a Blalock procedure could be carried out. In another patient the proximal portion of the pulmonary artery was atretic. Since additional blood could not possibly be shunted to the opposite lung by doing a Potts-Smith anastomosis, the distal end of the left main pulmonary artery was anastomosed end-to-side to the aorta. An exploratory thoracotomy was performed in two instances, anastomosis being impossible in view of the extensive pulmonary atresia which was found at surgery.

The diagnosis in tetralogy of Fallot and tricuspid atresia has been discussed previously.[3] The experience in this series has been quite similar except that all symptoms have been somewhat exaggerated. Cyanosis appeared quite early (table 1), especially in the infants with tricuspid atresia and in those with tetralogy of Fallot in which there was atresia of the pulmonary artery. Faint to definite clubbing of the fingers was present in 12 cases. The average weight gain was slower in the infants of this series and physical development was retarded. None of the children sat alone prior to surgery in spite of the fact that six of them were at least 8 months of age. Paroxysmal dyspnea was an outstanding symptom in this series, being present in 19 infants and constituting one of the major indications for surgery at an early age.

In this regard it should be emphasized that each of these patients was operated on only after the medical and surgical departments had agreed that intervention was mandatory if that patient were to survive. Each child was having repeated, severe attacks of paroxysmal dyspnea; or his weight was stationary or actually declining; or he was unable to live outside an oxygen tent even after protracted hospitalization.

The youngest child in this series was 12 days old and weighed 2.2 kg. at the time of surgery. The average age for the entire series was six months. The infant (R. B., #249), who was 12 days old when operated on, was a premature baby who weighed 2.3 kg. at

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From Children's Memorial Hospital, Chicago.
(Received for publication July 23, 1950.)

birth. He was moderately cyanotic at birth and required oxygen continuously. He took his feedings poorly, becoming quite exhausted after taking only one half ounce. He was having attacks of paroxysmal dyspnea and was becoming progressively weaker. A diagnosis of tricuspid atresia was made on the basis of cyanosis, decreased vascularity of the lung fields, a good pulmonary window and left heart strain in the electrocardiogram. The liver did not pulsate. Under ether anesthesia the chest was opened from a left posterolateral approach. As soon as the lung was collapsed the child manifested respiratory distress and the anesthesiologist found it necessary to insert an endotrachial tube in order to maintain the airway. The aorta was found to be 5 mm. in diameter and the pulmonary artery slightly smaller. In fact, the aorta was so tiny that even the smallest aortic clamp could not be used. As a result the surgeons were forced to improvise by simultaneously clamping off a portion

TABLE 1

HISTORY AND PHYSICAL EXAMINATION

	Tetralogy of Fallot (18 cases)*	Tricuspid Atresia (7 cases)
Average Birth Wt.	3.2 kg.	2.8 kg.
Average Wt. at Surgery	5.6 kg.	4.6 kg.
Average Age at Surgery	6½ mo.	5 mo.
Paroxysmal Dyspnea		
Present	12	7
Absent	6	0
Onset of Cyanosis		
Birth	4	5
Neonatal	5	1
1 mo.	3	0
2 mo.	4	1
After 2 mo.	2	0

* M. O. (#4) omitted because autopsy showed diagnosis to be incorrect.

of each vessel side by side in a single, curved, fine toothed forceps, after which the anastomosis was performed. During the procedure the condition of the infant necessitated stopping temporarily on two occasions while the left lung was reinflated. Atropine sulfate, gr. 1/1000, was administered intravenously on two occasions during surgery. Following the operation the color of the infant was markedly improved. He was placed on oral feedings within eight hours. Oxygen was administered for eight days. His temperature was normal 24 hours after surgery. A short systolic murmur was heard beneath the left clavicle the day following surgery, but a diastolic murmur was not heard until the eighth postoperative day. His general condition would have permitted discharge 14 days following surgery; however, he was kept in the hospital for one month while arrangements were being made for placement in a foster home. At the time of discharge he weighed 2.9 kg. There was no cyanosis apparent when he was quiet but he became mildly cyanotic upon crying. When seen in the outpatient clinic one week after discharge, he was getting

along very well. He now weighed 3.2 kg. and had been free from attacks of paroxysmal dyspnea. He was faintly cyanotic at rest. The heart was not enlarged and there was no evidence of cardiac decompensation.

Actual atresia of the pulmonary artery was demonstrated at surgery in four of the cases of tetralogy of Fallot (D. N., #221; R. D., #142; D. T., #242; B. A., #252). It is rather interesting that three of these patients either had no murmur preoperatively or had an atypical murmur. This would tend to confirm a previous impression that the typical murmur heard in tetralogy of Fallot is primarily due to the pulmonary stenosis rather than to the interventricular septal defect.[3]

An attempt was made in most of the cases to create an anastomosis which had a 4 mm. stoma (6¼ mm. linear incision). In one of the earliest cases, a 5 mm. stoma was attempted (M. O., #4). The smallest anastomosis was 3 mm. in diameter.

A surgical diastolic murmur was usually heard immediately following the operation; however, in one case such a murmur was not audible until the eighth postoperative day. In another patient (P. S., #53) a soft systolic-diastolic murmur was heard beneath the clavicle on the operated side the day following surgery. The murmur was no longer audible at the time of discharge from the hospital three weeks later, but a continuous murmur beneath the left clavicle was easily heard at the time of a routine visit 30 months after surgery. In three children there were no additional murmurs heard following surgery. In each such instance clinical or autopsy evidence showed that the anastomosis was not functioning. These cases will be discussed in more detail later.

Operative and Postoperative Complications

As previously mentioned two infants had atresia of the pulmonary artery and an anastomosis was impossible. In one case (D. T., #242), the parietal pleura was dissected out and the visceral pleura was scarified in an attempt to create new anastomotic channels between the lung and the chest wall; however, there was no obvious improvement in his condition following surgery. The second patient (B. A., #252) died before the chest could be closed. Postmortem examination revealed a transposition of the great vessels with a truncus aorticus solitarius, a large and a small defect in the interventricular septum, an auricular septal defect, mild tricuspid stenosis, hypertrophy of the right auricle and right ventricle and a small patent ductus arteriosus.

M. O. (#4) developed a pneumothorax postoperatively. Apparently the leak was occurring at the site of the incision, and so he was returned to surgery where the incision was reopened and then carefully closed. There was no further evidence of pneumothorax; however, he had a very stormy postoperative course and required oxygen for 27 days. There was no improvement in his preoperative symptoms following surgery and a diastolic murmur was never heard. A Blalock anastomosis on the other side was attempted three years later; however, he died 15 days after surgery. Autopsy examination revealed the presence of transposition of the great vessels with pulmonary stenosis and a large interventricular septal defect. The original anastomosis was completely thrombosed but the second anastomosis was patent.

In two additional patients a diastolic murmur was never heard following surgery. V. F. (#141) had repeated attacks of paroxysmal dyspnea and died 15 days postoperatively. There was no clinical evidence of heart failure at the time of death. Postmortem examination confirmed the diagnosis of tricuspid atresia and pulmonary stenosis. Moderate

sized defects were present in both the interauricular and interventricular septa. A thrombus occluded the left pulmonary artery just proximal to the anastomosis. The second infant (A. B., #148) manifested shock at the end of surgery. His liver enlarged and he had peripheral edema. His cardiac failure responded poorly to digitalization. After repeated attacks of paroxysmal dyspnea he died on the seventh postoperative day. Autopsy confirmed the diagnosis of tricuspid atresia and pulmonary stenosis. A small interventricular septal defect and a huge interauricular defect were present. The site of the anastomosis was thrombosed with slight extension distally into the left pulmonary artery.

Cardiac failure immediately following surgery also occurred in M. S. (#128). In spite of digitalis, the peripheral edema and enlargement of the liver and spleen progressed steadily until death on the sixteenth postoperative day. The findings at autopsy revealed the presence of a typical tricuspid atresia with a pulmonary stenosis, an interventricular septal defect, a very small defect in the auricular septum and marked passive congestion of the liver, spleen and kidneys.

M. P. (#71) developed major convulsions on the first postoperative day. A bronchopneumonia was thought to be present two days later. His cough, fever and pulmonary findings did not respond to penicillin, streptomycin or sulfadiazine and he died on the eighth day. Postmortem examination revealed the presence of a tetralogy of Fallot with moderate overriding of the aorta, fibrinous pleurisy and atelectasis on the operated side, mild pia-arachnoid hemorrhage over the right frontal lobe and massive central necrosis of the liver.

Three patients showed clinical evidence of bronchopneumonia postoperatively and died at 12 hours (S. R., #231), 36 hours (L. B., #233) and 14 days (T. K., #248), respectively. Autopsy confirmed the diagnosis of tetralogy of Fallot and bronchopneumonia in each case. There was no evidence of passive pulmonary congestion.

R. D. (#142) did not breathe spontaneously for two hours following surgery. Respirations were then very slow and finally ceased three hours later. Autopsy confirmed the diagnosis of tetralogy of Fallot. There was severe overriding of the aorta. The most significant finding was the presence of extensive thrombosis of the cerebral sinuses. Some of the thrombi appeared to have occurred several days prior to surgery. After a review of the clinical chart, it was concluded that completely adequate fluid intake was not maintained preoperatively.

Follow-up was made of the posthospitalization course in 10 of the 15 patients who survived surgery. Four infants have been observed for at least 24 months. One (R. R., #169) has been followed for 12 months; one (J. A., #140) for 15 months and one (L. S., #94) for 6 months. J. A. (#140) became mildly decompensated two weeks following surgery. He was digitalized and maintained on digitalis for two months. He was last seen 15 months after surgery, at which time his progress had only been fair. He was mildly cyanotic and tachypneic at rest. Moderate dyspnea and increased cyanosis occurred upon mild exercise. A grade III continuous murmur was audible beneath the right clavicle. Two children (J. C., #22; P. S., #53) show moderate cardiac enlargement upon physical and roentgenographic examination. All other patients show only mild cardiac enlargement. In these seven patients, cyanosis was either absent or faintly present at rest and was increased slightly upon exercise. Their physical tolerance was so markedly increased that they were able to exercise normally except for severe activity; however,

mild exertional dyspnea was still present in all cases. The phenomenon of paroxysmal dyspnea has not been observed in any patient with a successful anastomosis. Three patients have been followed for less than two months and cannot be satisfactorily evaluated; however, their course so far has been similar to the preceding cases.

Discussion

The mortality in this series is admittedly high when compared with that observed in the older age groups operated by the same surgical team (table 2). Two important factors influence this difference in the mortality rate. First, the smaller size of the blood vessels in these infants made surgical repair much more difficult. Not only were they under anesthesia longer than usual, but the anastomosis was more likely to close. Second,

TABLE 2

Mortality Statistics in Anastomosed Cases

Age	No. of Cases	Deaths	Per Cent Mortality
0–1	24	8	33.3
1–2	33	6	18.2
2–3	38	5	13.2
3–16	139	4	2.9
Total	234	23	9.8

and more important, these children were poor operative risks since surgical intervention was not considered unless their outlook seemed hopeless otherwise. The consensus was that they could not survive even a few months, much less to the optimum age of 4 to 7 years. The high mortality would seem to be justified in order to alleviate symptoms and prolong life in 67% of operated cases.

Summary

Since September 1946, surgical relief for tetralogy of Fallot or tricuspid atresia has been performed in 234 instances. During this period an anastomosis has been created in 24 infants under 1 year of age. Pulmonary atresia prevented an anastomosis in two additional infants. In those children in whom an anastomosis was possible, the mortality was 33.3% under 1 year of age as compared to an over-all mortality of 9.8%, with a mortality of only 2.9% between the ages of 3 and 16 years.

The reasons for this higher mortality in infants are explained and surgical relief in selected cases is recommended.

References

1. Blalock, A., and Taussig, Helen B., Surgical treatment of malformation of heart in which there is pulmonary stenosis or pulmonary atresia, J.A.M.A. **128**:189, 1945.
2. Potts, W. J., Smith, S., and Gibson, S., Anastomosis of aorta to pulmonary artery, J.A.M.A. **132**:627, 1946.
3. Dammann, J. F., Jr., Gibson, S., and Potts, W. J., Observations on 117 patients operated on for congenital pulmonary stenosis, Pediatrics **3**:575, 1949.

SPANISH ABSTRACT

Observaciones en 26 Niños Menores de un Año de Edad Operados por Tetralogia de Fallot o por Atresia Tricuspidea

Los autores indican que desde septiembre del año 1946, un total de 234 operaciones han sido realizadas en pacientes con tetralogia de Fallot o de atresia tricuspidea. Durante ese periodo, una anastomosis fué realizada en 24 niños menores de un año de edad. En los otros dos casos, la creación de una anastomosis fué imposible debido a una atresia pulmonar. La mortalidad en el grupo de niños operados menores de un año de edad fué de 33.3%. La mortalidad total para todas las edades fué de 9.8%; con una mortalidad de 2.9% para el grupo de 3 a 11 años de edad.

Los autores explican las razones de la mortalidad alta en pacientes menores de un año de edad, recomendando el tratamiento quirurgico solamente en casos seleccionados.

707 West Fullerton Avenue

ACUTE PURULENT ARTHRITIS (B. PYOCYANEUS) IN A PREMATURE INFANT

Recovery with Streptomycin

By JAMES M. COLEMAN, M.D., AND FREDERICK C. LOWRY, M.D.
Austin, Texas

SUPPURATIVE arthritis, secondary to B. pyocyaneus, is exceedingly rare. Stanley,[1] in a review of pyocyaneus infections reported in the literature, found only eight cases of bone and joint involvement resulting from this organism and, of these, only five were arthritis.

The present report is of an acute pyogenic arthritis, attributed to B. pyocyaneus, in a premature infant. Apparently, no case has been reported of pyocyaneus infection in a premature infant, nor has a case been reported of pyocyaneus arthritis treated with streptomycin. Also, the fact that the patient responded favorably to treatment with streptomycin added significance to these findings.

M. N., a female premature infant, weighed 2,043 gm. at birth and appeared to be in good condition. Her mother had had no prenatal care and had arrived at the hospital in labor. Delivery was accomplished without difficulty. Wassermann test for syphilis made on the mother's blood, following delivery, was negative.

The infant was given vitamin K and was placed in an incubator. After 24 hr., boiled water was offered and taken by nipple. At 48 hr., she was placed on a formula of evaporated milk, water and Karo every 3 hr. She took the formula rather poorly, however, and on the fourth day had evidences of mild dehydration. On each of the following 6 days, she was given 50 cc. of 5% glucose in water by hypodermoclysis. On the 9th day of life, the infant was found to have a typical thrush of the buccal mucosa. She was isolated and treated locally with 2% gentian violet, with prompt clearing of the lesions. From the 12th to the 16th days, she took feedings well and gained from 30 to 60 gm. daily. On the 14th day, the child's temperature was 37.7° C., but physical examination revealed no abnormality. On the 15th day, the temperature was 38.3° C., and the following day, 38.9° C. The infant was extremely irritable, the slightest movement obviously causing extreme pain, and the right knee was held in acute flexion, with marked swelling localized in the joint and evidence of fluid. Forceful extension of the joint caused pain.

Roentgenograms revealed soft tissue swelling about the knee joint, without evidence of a destructive lesion in the bones. The knee was aspirated on the 16th day of life and 5 cc. of a watery, turbid fluid were removed, smears of which were negative for bacteria to the Gram's stain.

Cultures of the fluid taken on the 16th day of life showed growth in all cultures the following day and a smear from these showed gram-negative bacilli. The child was placed on combined soluble crystalline and repository penicillin, 400,000 units, twice a day, but this was discontinued on the 17th day of life and the patient placed on dihydrostreptomycin 0.5 gm. every 12 hr. The following day, subcultures of the joint fluid were reported as showing B. pyocyaneus.

At this time, the patient's temperature was 37.7° C. and the knee had marked swelling which appeared to be fluctuant. Under local anesthesia, a needle was introduced into the joint, and 2 cc. of watery, green pus were aspirated. The joint was then irrigated with a solution of streptomycin 250 mg. in 30 cc. of distilled water. About 3 cc. of fluid were allowed to remain in the joint. A single hip spica bandage was applied with the hip in slight flexion and with the knee in as much extension as was possible (160°).

Cultures of the fluid obtained on the second aspiration showed B. pyocyaneus.

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(Received for publication Aug. 11, 1950.)

Dihydrostreptomycin was continued in dosages of 0.5 gm. every 12 hr. On the 19th day of life, the temperature became normal and remained so. The streptomycin was discontinued on the 23rd day of life and 4 days later the cast was removed. RG of the knee on this date showed no evidence of bone involvement. When the infant was 2 mo. old, the knee appeared perfectly normal and there was a complete range of active motion.

Discussion

Epstein and Grossman[2] call attention to the serious and often fatal import of B. pyocyaneus infections in infants and children. Wassermann is said to have reported an epidemic of 11 cases of umbilical infection with sepsis in infants in which all cases terminated fatally. It would appear on the basis of the response in this case that streptomycin may affect the mortality of this condition favorably.

The source of the joint infection is open to speculation. Entry of the organism conceivably may have occurred through the umbilical cord, but this portal was healed when the joint involvement appeared. It is possible that the thrush infection was a mixed infection with breaks in the mucous membrane permitting entry of the organism. The skin was broken for hypodermoclysis on several occasions, but no local reaction or abscess appeared at the sites of injection.

Summary

A pyogenic arthritis, acute in character, in which B. pyocyaneus was the infecting organism, occurred in a premature white female infant confined to an incubator from birth. The infection cleared rapidly with the administration of dihydrostreptomycin intramuscularly. Its use in irrigating the joint at the time of aspiration may have aided in therapy. On the patient's discharge from the hospital, she seemed normal in every respect.

References

1. Stanley, M. M., Bacillus pyocyaneus infections, Am. J. Med. **2**:253 and 347, 1947.
2. Epstein, J. W., and Grossman, A. B., Bacillus pyocyaneus in children, Am. J. Dis. Child. **46**:132, 1933.

Spanish Abstract

Artritis Purulenta Aguda (B. pyocyaneus) en un Prematuro Tratada con Estreptomicina

Una artritis purulenta aguda, en la cual el organismo infectante fué el B. pyocyaneus, ocurrió en un prematuro confinado en la incubadora desde el nacimiento. La infección desapareció rapidamente con la administración intramuscular de dehidroestreptomicina. El autor estima que la irrigación de la articulación con estreptomicina siguiente a la aspiración del pus puede haber contribuido al éxito del tratamiento. A la salida del hospital, el paciente aparecia normal en todos las respectos.

1506 Guadalupe Street

TERRAMYCIN HYDROCHLORIDE IN THE TREATMENT OF SALMONELLA CHOLERAESUIS BACTEREMIA

By ROLAND B. SCOTT, M.D., AND CLINTON H. WOODING, JR., M.D.
Washington, D.C.

TERRAMYCIN* is a new antibiotic derived from the soil actinomycete, Streptomyces rimosus. The organisms which are susceptible to its inhibitory powers represent a wide variety of bacteria and include certain of the gram-negative bacilli.

In experimental studies, the antibiotic has proved effective against susceptible organisms when administered parenterally or orally and also exhibits a low degree of toxicity.[1]

This report deals with the use of terramycin in children infected with Salmonella choleraesuis.

CASE REPORTS

Case 1. (Chart 1.) L. R., a 2 yr. old Negro female, entered the hospital with the complaints of severe cough, dyspnea, lethargy, frequent stools, vomiting and anorexia. She had been ill for 8 days. Four days prior to admission these symptoms began to increase in severity, becoming most marked in

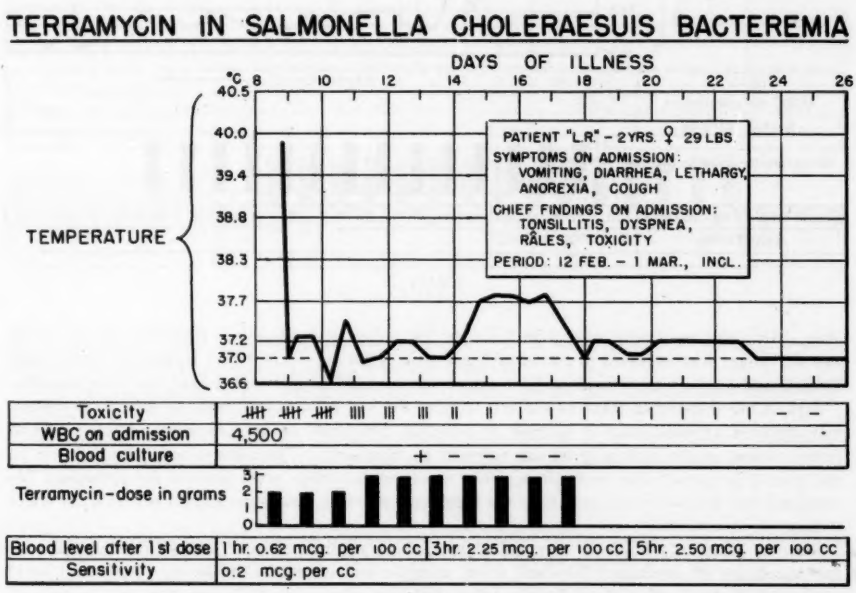

CHART 1

From the Department of Pediatrics, Howard University School of Medicine, and the Pediatric Service of Freedmen's Hospital, Washington, D.C.

(Received for publication May 1, 1950.)

* Manufactured by Chas. Pfizer & Co., Inc., Brooklyn.

the last 48 hr. Chief findings on admission were fever (39.9° C.), hyperemia of the tonsils and oral pharynx, rapid respiration, dullness to percussion in the left posterior chest and scattered rales throughout both lungs.

Laboratory data: Hemogram: RBC 3.9 million/cmm.; Hgb. 12.5 gm./100 cc.; WBC 4.5 thousand/cmm.; differential: 42% neutrophils and 58% lymphocytes. Blood Kahn reaction and tuberculin patch test were negative. Urinalysis was normal. Chest roentgenogram revealed severe bronchitis and pneumonitis in the right lung.

At the time of this child's admission terramycin hydrochloride was being investigated for various infectious diseases. Because of the obvious respiratory infection, the patient received 2 gm. of the

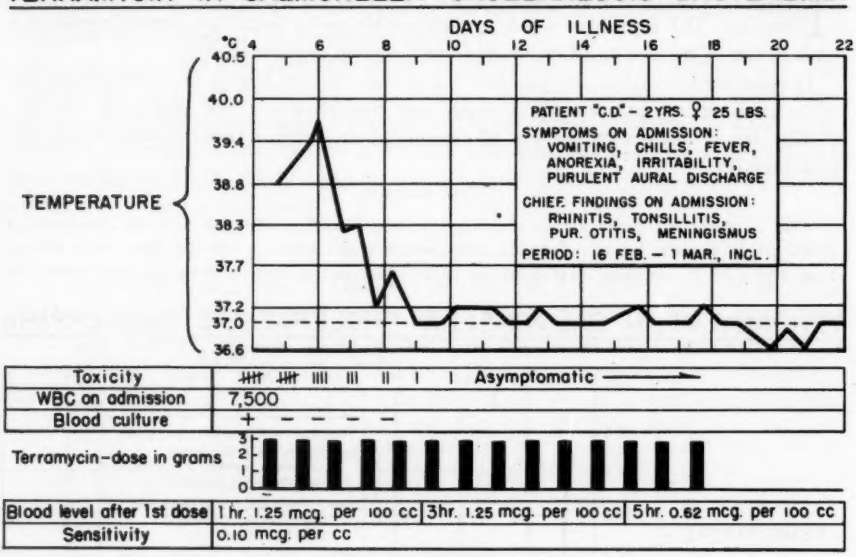

CHART 2

drug daily (330 mg. orally every 4 hr.) for the 1st 3 days in the hospital. Beginning on the fourth day the dosage was increased to a total of 3 gm. daily (500 mg. every 4 hr.) because of contact with Cases 2 and 3 who were thought to have enteric infections. This increased dosage was maintained for 7 days. A blood specimen taken on the first hospital day just prior to institution of terramycin therapy was reported as unsatisfactory because of technical difficulties in the laboratory. A repeat blood culture taken on the fifth hospital day revealed S. choleraesuis. Thereafter blood cultures taken on the next 4 successive days were all negative. Stool cultures were never positive for pathogens. No untoward reactions were observed from the treatment. However, moderate toxicity persisted for about 9 days.

Case 2. (Chart 2.) C. D., a 2 yr. old Negro female, cousin to Case 1, entered the hospital with the complaints of vomiting, chills and fever, anorexia and irritability. There was a purulent nasal and aural discharge of 4 days' duration. On admission, physical examination revealed evidence of rhinitis, bilateral otitis media, tonsillitis, bronchitis and meningismus.

Laboratory data: Hemogram: RBC 3.9 million/cmm.; Hgb. 12 gm./100 cc.; WBC 7.5 thousand/cmm.; differential: 38% neutrophils, 61% lymphocytes and 1% eosinophils. The blood Kahn reaction and tuberculin patch test were negative. Chest RG was compatible with a diagnosis of extensive bronchitis. The urine and cerebrospinal fluid were normal.

A blood culture taken on the day of admission revealed S. choleraesuis. Subsequent cultures were negative. Stool cultures were never positive for pathogens.

Terramycin hydrochloride 3 gm. was administered orally daily for 13 days. No untoward reactions were observed. Clinical improvement was progressive and she was asymptomatic after the 15th hospital day.

Case 3. (Chart 3.) L. D., a 4 yr. old Negro male, brother to Case 2, entered the hospital with the complaints of vomiting, anorexia and mucopurulent nasal discharge of 5 days' duration. Chief findings on admission were mild convulsive seizure, right facial paralysis (transient), catarrhal otitis media, tonsillitis, nuchal rigidity and positive Kernig sign.

Laboratory data: Hemogram; RBC 4.2 million/cmm.; WBC 9.5 thousand/cmm.; differential:

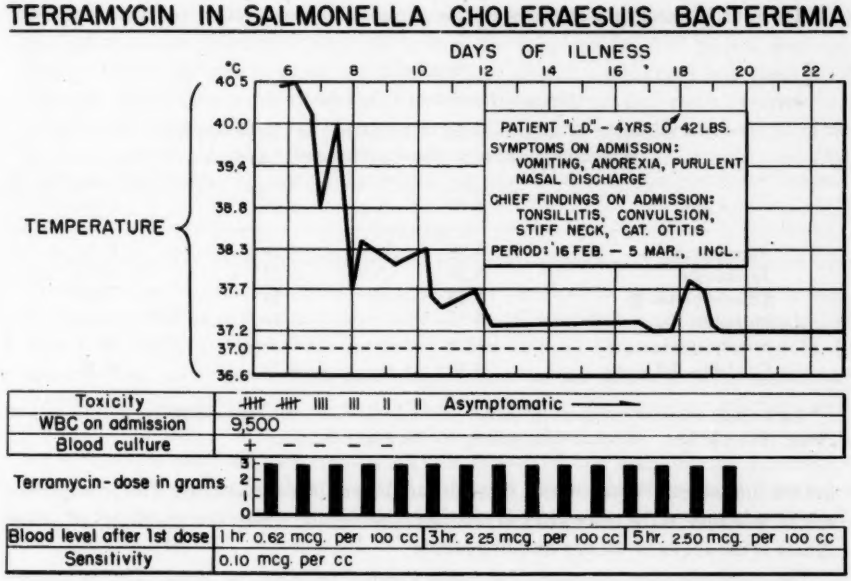

CHART 3

41% neutrophils, 58% lymphocytes and 1% eosinophils. Blood Kahn reaction and tuberculin patch test were negative. Urine and cerebrospinal fluid were negative.

The admission blood culture was positive for S. choleraesuis. All stool cultures were negative for pathogens.

This patient received a daily oral dose of terramycin hydrochloride 3 gm. for 15 days. No untoward reactions were observed. Clinical improvement was progressive and recovery uneventful.

DISCUSSION

The organisms which were recovered from the blood of the three cases reported here were identified serologically as S. choleraesuis (var. Kunzendorf, VI, VII: [c]: 1, 5). Initial blood cultures were positive in all the cases. All stool cultures were negative for pathogens. These patients represented the septicemic type of salmonella infection. Cases 2 and 3 responded promptly to therapy but Case 1 appears to have responded only after an increased dose of the drug was given. All patients made uneventful recoveries.

Sensitivity studies (table 1) showed that the organisms isolated from these patients

were more susceptible to terramycin than to streptomycin, aureomycin, chloromycetin® and polymyxin®. Comparable results, however, were obtained with combiotic®.*

S. choleraesuis (suipestifer) infection in children produces three types of disturbances: a typhoid-like fever, an acute gastroenteritis and a bacteremia (septicemia). In the past the gastroenteric type has been most often encountered; however, the septicemic type is now being reported with increasing frequency.[2] Since members of the Salmonella group may cause a wide variety of symptoms, Bornstein[3] does not place too much emphasis on separation of the Salmonella organisms into specific groups producing set patterns. In children this tends to be especially applicable.

Man usually becomes infected with this organism through eating contaminated foods

TABLE 1

MINIMAL INHIBITORY CONCENTRATION

Sensitivity of S. Choleraesuis to Terramycin as Compared with Sensitivity to Other Antibiotics (measured in μg./cc.)

Cases	L.R.	C.D.	L.D.
Aureomycin	0.39	0.39	0.39
Terramycin	0.20	0.10	0.10
Chloromycetin ®	1.46	1.56	1.56
Polymixin ®	0.76	0.39	0.39
Streptomycin	+25.0	+25.0	25.0
Combiotic ®*	0.10	0.20	0.10

* Each tablet contains streptomycin sulfate, 250 mg. (as base), bacitracin, 5000 units; polymixin B, 20 mg. (Pfizer & Co.). (Product subsequently modified for clinical use.)

but the disease may be transmitted through handling of infected animals. The pathogenesis of the infection in the three cases in this report is obscure. There was no history of recent illness in the adults of the city dwelling family.

The predominating symptoms are either enteric, pulmonic or septic. The incubation period varies from a few hours to several days. Symptoms include headache, nausea, vomiting, fever, diarrhea, meningismus and occasional enlargement of the spleen. Either leucopenia or leucocytosis may occur. The duration of the disease is variable and usually shorter than in typhoid fever.

The diagnosis is a bacteriologic one and consists of isolation from the blood, urine, stool or pus of the organisms and the demonstration of an increased agglutination titer in the patient's serum. Identification is dependent upon serologic typing and sugar fermentation tests.

Septic localization of the organisms accounts for the majority of the complications of arthritis, meningitis and abscesses. Bronchitis is often seen in the early stages and bronchopneumonia may be a complication also.

The treatment of S. choleraesuis infection has been unsatisfactory. Bornstein[3] states

* Each tablet contains streptomycin sulfate, 250 mg. (as base), bacitracin, 5000 units; polymixin B, 20 mg. (Pfizer & Co.). This product is now commercially available in modified composition: crystalline procaine penicillin G 300,000 units, buffered crystalline sodium penicillin G 100,000 units and dihydrostreptomycin sulfate 1 gm.

that S. choleraesuis is more susceptible to the sulfonamides than are the other Salmonella organisms. Neter and Krauss[4] report a case of a 10 year old child with S. choleraesuis bacteremia complicating a streptococcal sore throat. He was treated with sulfadiazine and made a complete recovery; however, the authors did not attribute the recovery to the sulfonamide. Jones and Lee[5] found different sulfonamides, singly and in combination, to be ineffective in 18 cases in children. Selby and Tidler[6] treated a fatal case in a 53 year old Negro female with both streptomycin and penicillin, neither of which proved to have any effect on the organism or the presenting symptoms.

Collins et al.[7] reported the case of a 68 year old white male who was acutely ill and in poor condition on admission. Blood cultures obtained before and during 11 days of oral and intramuscular aureomycin were all positive for S. suipestifer. The patient died suddenly due to a ruptured aneurysm of the abdominal aorta. S. choleraesuis was recovered at necropsy from cultures of blood and pus from intervertebral and psoas abscesses and from several organs. There was no apparent beneficial effect from the aureomycin on the local or systemic infection. Streptomycin was also given during the last four days without appreciably influencing the course of the infection.

Summary

Three cases of S. choleraesuis bacteremia have been presented. They were treated with terramycin, a new antibiotic. Encouraging results were obtained in all cases. The average duration of toxicity and temperature (above 37.2°C. rectally) was approximately five days after administration of the antibiotic. Blood cultures became negative within 48 hours in two cases. In the other case blood culture on the fifth day of treatment was positive but four subsequent daily cultures were negative. No untoward reactions were observed. The drug was readily accepted when administered orally. Though appraisal of the therapeutic effect of terramycin is difficult because of the variability of duration of the untreated disease, it would appear that terramycin may be superior to the sulfonamides and to the other currently available antibiotics in the treatment of S. choleraesuis septicemia in children.

Acknowledgments

For identification of the salmonella organism the authors are indebted to: Bacteriology Division of the Naval Medical Research Institute, National Naval Medical Center, Bethesda, Md.; Salmonella Center, Beth Israel Hospital, New York; Mrs. Lauritta W. Morris, Chief Bacteriologist, Freedmen's Hospital, Washington, D.C.; Communicable Disease Center, Enteric Bacteriology Laboratories, Chamblee, Ga.; Public Health Service, FSA.

Addendum

At the time when these cases were being studied, only the oral route of administration was recommended for the clinical use of terramycin. Crystalline terramycin hydrochloride parenteral (intravenous) was recently released for clinical use.

References

1. Finlay, A. C., and others, Terramycin: New antibiotic, Science **3**:85, 1950.
2. Bradford, W., in Mitchell-Nelson Textbook of Pediatrics, ed. 5, edited by W. E. Nelson, Philadelphia, W. B. Saunders Company, 1950, p. 528.
3. Bornstein, S., State of Salmonella problem, J. Immunol. **46**:439, 1943.
4. Neter, E., and Krauss, R. F., Salmonella choleraesuis (variety Kunzendorf) bacteremia complicating streptococcal sore throat, J. Pediat. **28**:422, 1946.

5. Jones, J. A., and Lee, H. F., Salmonella suipestifer infection in children: Report of 18 cases, Am. J. M. Sc. **211**:723, 1946.
6. Selby, J., and Tidler, J., Salmonella choleraesuis bacteremia treated with streptomycin, M. Ann. District of Columbia **18**:134, 1944.
7. Collins, H. S., Paine, T. F., Wells, E. B., and Finland, M., Aureomycin: New antibiotic; evaluation of its effect in typhoid fever, severe Salmonella infections and in case of colon bacillus bacteremia, Ann. Int. Med. **29**:1077, 1948.

SPANISH ABSTRACT

Terramicina en el Tratamiento de la Salmonelosis (S. choleraesuis)

La terramicina es un nuevo antibiotico derivado del Streptomyces rimosus. Este antibiotico tiene acción inhibitoria sobre numerosas variedades de bacteria incluyendo bacilos negativos al gram. Por el momento, solo la ruta oral de admistración es recomendada. Este reporte se relaciona con el uso de la terramicina en tres niños infectados con Salmonela choleraesuis. Todos los pacientes estaban seriamente enfermos, con apariencia toxica y presentando un cuadro clinico caracterizado por fiebre, vómitos, diarrea y anorexia. En todos los pacientes se obtuvo hemocultivos positivos con Salmonela Choleraesuis. La dosis de terramicina varió entre dos y tres gramos diarios.

Los resultados del tratamiento fueron favorables en todos los casos. La fiebre y toxicidad general cedió a los cinco dias de tratamiento con terramicina. El hemocultivo fué negativo en las primeras 48 horas en dos casos y al quinto dia en el otro paciente. No se observaron reacciones tóxicas con el uso oral de la droga.

Los autores consideran las dificultades en la evaluación de los efectos terapeuticos de la terramicina, particularmente debido a la variabilidad del curso clinico de la enfermedad sin tratar. Sin embargo, estas observaciones parecen indicar que el uso de la terramicina puede ser superior a las sulfonamidas ú otros antibioticos en el tratamiento de la septicemia debida a la Salmonela choleraesuis.

Sixth and Bryant Streets, N.W.

DIPLOCOCCUS CRASSUS SEPTICEMIA IN A PREMATURE INFANT

By HUGO M. CARDULLO, M.D., IRVING SCHULMAN, M.D., AND FRANCES CAPRON SMITH, M.D.
New York

THE unusual clinical picture seen in Diplococcus crassus septicemia occurring in a premature infant and the bacteriologic properties of this organism as revealed by a study of the literature[1-27] have stimulated the present report. Although cases of infection due to this micro-organism are not uncommon in Europe (table 1), not a single instance has been reported from American sources.

CASE SUMMARY

E. B. (B.H. 75351-49), a vigorous and alert prematurely born female infant, was the fourth child of a 26 yr. old woman who received antiluetic treatment during the first trimester of pregnancy. Gestation terminated spontaneously at approximately 28 wk.; weight at birth was 930 gm. After an initial loss of 90 gm., the baby gained steadily and her hospital course was uneventful except for a moderately severe anemia which was improved by several whole blood transfusions. Repeated Wassermann tests were negative in both mother and child.

On the 84th day of life, the patient weighed 2250 gm. and was thought ready for discharge. The following day, however, her temperature rose to 39.6° C., she was lethargic, her cry was weak and her general appearance poor. The only abnormal physical findings were a moderate distension of the abdomen and a definite increase in size of the liver to 2.5 cm. below the costal margin whereas it had previously been barely palpable. Examination of the blood showed: Hgb. 6.9 gm., WBC 7 thousand/cmm., polymorphonuclears 37, immatures 12, lymphocytes 45. Urine examination was negative.

A tentative diagnosis of septicemia was made. Accordingly, after obtaining blood, nose, throat and stool cultures, aureomycin (60 mg./kg.) and sulfadiazine (100 mg./lb.) were started and a whole blood transfusion (45 cc.) given. Later in the day when the infant began to vomit, parenteral penicillin (100,000 units every 8 hr.) was added since this complication made the effectiveness of oral antibiotic therapy uncertain.

By evening although the temperature had fallen to approximately normal, a generalized lymphadenopathy with moderate splenomegaly had appeared. The adenopathy was most marked on the right, especially the anterior cervical chain and the axillary group where the individual nodes were the size of large walnuts. There was no associated heat or redness and no apparent tenderness.

The next morning both blood culture flasks yielded large numbers of cocci which tended toward a diploid arrangement. Most of the cocci were gram-positive but fully one third were gram-negative. Stool cultures were negative. From the nose and throat, H. Staph. aureus, Staph. albus, B. coli and alpha Strep. were isolated. The patient's general state meanwhile remained essentially the same except that the submandibular, cervical and axillary nodes on the right side had further increased in size, although they were still discrete, freely movable and nontender. The liver was now palpable at the level of the umbilicus and the spleen had enlarged to 1 cm. below the costal margin. Vomiting had completely ceased and the baby fed hungrily. The temperature ranged about 37.8° C.

On the third day marked improvement was apparent. The abdominal distension was decidedly less, the liver edge had receded to 1.5 cm. below the costal margin and the adenopathy had diminished appreciably. The baby's breathing, which had been labored, was easier and the respiratory rate was

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slower. However, no cause could be found for the bloody mucoid nasal discharge which appeared at this time. The total WBC, differential and thrombocyte counts were normal. The Hgb. had risen to 9.5 gm./100 cc. Vitamin K (5 mg.) was administered intramuscularly and a second blood transfusion (25 cc.) was given.

Repeated blood cultures were sterile, but smears of the colonies grown on the pour plates made from the initial positive cultures showed both gram-positive and negative diplococci.

TABLE 1

SUMMARY OF PUBLISHED CASES[1-27] OF D. CRASSUS INFECTIONS

Author	Form of Infection	No. of Cases	Age	Result
1. Jäger, H.	Meningitis	14	Adults	10 Deaths
2. Heubner, O.	Meningitis	6	Adults	—
3. von Lingelsheim, W.	Meningitis	26	Adults	—
4. Harvier, P.	Meningitis	1	Newborn	Death
5. Mosny, E., and Portocalis, F.	Pneumonia	3	Adults	1 Death
6. Biscons, R.	Septicemia with Meningitis	1	21 yr.	Recovery
7. Sacquepee, L., et al.	Meningitis	40	Adults	—
8. Botez, M. H.	Meningitis and Cerebral Abscess	1	—	Death
9. Sabrazes, J., et al.	Meningitis	1	28 yr.	Recovery
10. Forbes, J. G.	Meningitis	1	50 yr.	Death
11. Chevrel, M.	Meningitis	2	Newborn	2 Deaths
12. Georgiu, I.	Septicemia	—	Children and Adults	—
13. Railliet, M., et al.	Septicemia and Meningitis	1	7 yr.	Recovery
14. Harvier, P., and Cattan, R.	Septicemia, Meningitis with Fulminating Purpura	1	34 yr.	Death
15. Fiorio, C.	Pseudomembranous Tonsillitis	1	Child	Recovery
16. Lévy-Bruhl, M.	Mastoiditis (30), Septicemia (6), Meningitis (3)	39	—	—
17. Chevallier, P., et al.	Septicemia (4), Lymphadenopathy (3), Mucocutaneous Lesions (1)	4	Adults	Recovery
18. Colombe, J., and Sauvage, F.	Meningitis	1	2½ mo.	Death
19. De Toni, G., and Gallerani, U.	Pyelocystitis	1	Child	Recovery
20. Dondi, G.	Septicemia and Meningitis	1	8 yr.	Death
21. Sabatelli, F.	Terminal Septicemia	1	60 yr.	Death
22. Moreau, R., et al.	Septicemia with Endocarditis	1	54 yr.	Death
23. Marcoff, K.	Positive Tonsillar Culture	1	—	—
24. Nasilowsky, A.	Meningitis and Septicemia	2	5 and 8 mo.	Recovery
25. Bordes, L., et al.	Meningitis	1	8 yr.	Death
26. Chevrel, F.	Meningitis	1	21 yr.	Recovery

The micro-organism was identified as D. crassus on the basis of its cultural, morphologic and sugar fermentation reactions. It was sensitive to 10 mg./cc. sulfadiazine, 36 μg./cc. aureomycin and 10 u./cc. penicillin. The blood sulfadiazine level at this time was 15 mg./100 cc.

The fourth day after the onset of the illness, crops of indurated, red, lentil-sized nodular lesions appeared on both arms and legs. Some were smooth, others were surmounted by a yellow-white pustule and a few showed early scab formation. Several of these were opened and cultured, but proved to be sterile. On the left arm and leg scattered petechiae were seen and it was noted that fairly marked edema had developed in these extremities. Despite these new developments and the continua-

tion of the bloody nasal discharge, the baby continued to show general improvement. The cervical lymphadenopathy had completely disappeared, the axillary nodes were barely palpable and the spleen could no longer be felt. The temperature remained normal. Roentgenograms of the chest and long bones were normal, and cultures of the spinal fluid were repeatedly sterile.

At this point sulfadiazine was discontinued because of a fall in the total white cell count to 3.3 thousand/cmm., with neutropenia and relative lymphocytosis.

Over the next few days the skin lesions cleared rapidly and the peripheral edema gradually subsided. The nasal bleeding ceased and, 3 days after discontinuation of the sulfadiazine, the WBC had risen to 10.4 thousand/cmm. with a normal differential. Two weeks after the onset of the illness the infant showed no residual pathologic findings on physical examination and she was discharged fully recovered weighing 2600 gm.

Discussion

D. crassus is a member of the Neisseria family of organisms which includes (in addition to the commoner meningococcus, gonococcus and catarrhalis) D. siccus, D. mucosus, D. flavus I, II, and III and D. cinereus. As a group they are considered to be of low virulence and are fairly frequently encountered in the nasopharynx of normal individuals. They may, however, become pathogenic by invading the blood and/or the central nervous system. De Toni, as quoted by Dondi,[21] notes that particularly in infancy, where resistance is low, these organisms often assume marked virulence. In this respect D. crassus is the most frequent offender as is attested by the numerous reports in the literature of meningitis and septicemia as well as the more isolated cases of pneumonia, otitis, mastoiditis, lymphadenitis, cerebral abscess, tonsillitis, purpura and pyelocystitis due to this organism (table 1).

An analysis of the reported cases showed that, of a total of 152, only 11 occurred in infants and children, in none of whom was there any coexisting illness. It would have seemed from reports in table 1[3,4,6,8,11,18,22,23] that D. crassus infections occur less frequently in previously healthy individuals than in persons who are debilitated or chronically ill. Sacquepee[8] mentions 40 cases of meningitis in which D. crassus was encountered alone or with other pyogens but he does not specify the exact number in which mixed infections occurred. When these are subtracted from the total, there remain 112 analyzable instances of infections due to D. crassus. Inasmuch as some additional pathologic process or agent was encountered in only nine cases, D. crassus was solely responsible for disease in 103 or approximately 92% of the cases. It seems likely, therefore, that the virulence of D. crassus varies from time to time.

At present the factors responsible for this alteration of virulence are not known. Chevallier, Lévy-Bruhl and Bernard[18] found that mice, guinea pigs and rabbits were resistant to infection with D. crassus injected intravenously, intraperitoneally or intracerebrally. Harvier[5] reported that rabbits did not develop meningitis following the intracerebral injection of D. crassus unless the animals had previously been sensitized by intravenous inoculation of the bacteria. Similarly, healthy mice were unaffected by the micro-organism but mice previously made to inhale chlorine died shortly of septicemia.[28] On the other hand, with D. crassus isolated directly from a patient dying of meningitis, Bordes et al.[26] caused a fatal meningitis in a monkey by means of intracerebral inoculation.

Although the illness may begin insidiously in adults, with a symptomatology so vague as to lead to a suspicion of malingering,[18] in infants and children the onset is abrupt.[5,12,14,16,19-21,25,26] In the premature infant herein reported, fever, hepatosplenomegaly and slight abdominal distention were the first indications of disease. It should be borne in mind, however, that premature infants may respond to sepsis with such indefinite symptoms as anorexia, debility, listlessness or restlessness. Fever is often absent.

The course of the illness is usually quite long, ranging from 10 to 45 days, even in patients treated with sulfonamides,[25,27] and is often characterized by the presence of an irregular fever which some have called "paratyphoid,"[13] "pseudotyphoid"[12] or "typhoid-like."[23] The reference of Chevallier et al.[18] to lymph node involvement is of interest in view of the marked lymphadenopathy found in the patient reported here. They reported that D. crassus was isolated from the lymph nodes of three patients, all of whom had venereal infections. It was postulated that the micro-organism has a predilection for lymphoid tissue where it may reside without causing symptoms until the body is invaded by more active pathogens (i.e., spirochetes), at which time the virulence of D. crassus is augmented. The adequate antiluetic therapy given the mother early in pregnancy and the negative serology in both mother and child at the time of birth eliminate syphilis as a possible precipitating factor. It seems more likely that an acute invasion of lymphoid tissue occurred following the initial bacteriemia and that this resulted in extensive lymph node involvement.

Sensitivity studies point to sulfadiazine as the most effective of the three agents employed in combating this infection. However, it is difficult to discount the effect of the antibiotics. There is strong reason to believe that it was the prompt institution of combined therapy which resulted in the rapid and complete recovery of the patient.

Summary

A report is made of a case of D. crassus septicemia in a premature infant characterized by sudden onset and marked lymph node involvement with recovery following the use of combined chemotherapy.

Acknowledgment

The authors wish to thank Dr. Ann G. Kuttner for her many valuable suggestions and Miss Lotte R. Weilheimer for her technical assistance.

References

1. Jäger, H., Zur Ätiologie der Meningitis Cerebrospinalis Epidemica, Ztschr. f. Hyg. **19**:351, 1895.
2. Heubner, O., Zur Ätiologie und Diagnose der epidemischen Cerebrospinal meningitis, Deutsche med. Wchnschr. **27**:423, 1896.
3. von Lingelscheim, W., Die bakteriologischen Arbeiten der Kgl. Hygienischen Station zu Benthen O. Schl. während der Genickstarreepidemie in Oberschlesien im Winter 1904-1905, Klin. Jahrb. **15**:373, 1906.
4. von Lingelsheim, W., Beiträge zur Ätiologie der epidemischen Genickstarre nach den Eigebnissen der letzen Jahre, Ztschr. f. Hyg. u. Infektionskr. **59**:456, 1908.
5. Harvier, P., Méningite à D. Crassus, Compt. rend. Soc. de biol. **71**:266, 1911.
6. Mosny, E., and Portocalis, F., Trois cas de pneumonie pseudolobaire, J. de physiol. et de path. gén. **13**:241, 1911.
7. Biscons, R., Un cas de sépticemie à Diplococcus Crassus avec localisation méningée cerebrospinale, Paris méd. **13**:212, 1913-1914.
8. Sacquepee, L., Burnet, G., and Weissenbach, R., Rémarque sur les méningites aigües chez les troupes en campagne, Bull. Acad. de méd. **74**:103, 1915.
9. Botez, M. H., Méningite et abscès cérébrale ayant comme agent causal le diplococque Jäger-Heubner, Compt. rend. Soc. de biol. **78**:487, 1915.
10. Sabrazes, J., Piechaud, F., and Moreau, N., Méningite grave à Diplococque prenant le Gram: traité avec succès par un autovaccin et par des injections intrarachidiennes d'étain colloidal, Gaz. hebd. d. sc. méd. de Bordeaux **22**:254, 1919.
11. Forbes, J. G., D. Crassus and meningitis associated with case of fractured base of skull, Lancet **2**:690, 1920.

12. Chevrel, M., Méningites cérébrospinales à pseudomeningococques chez le nourrisson, Bull. et mém. Soc. méd. d. hôp. de Paris **46**:1742, 1922.
13. Georgiu, I., Sur quelques cas de septicémie à D. Crassus, Compt. rend. Soc. de biol. **88**:535, 1923.
14. Railliet, M., Techoueyres, Ginsbourg, and Pillement, Mlle., Septicémie à D. Crassus avec méningite suppurée et fiévre pseudopoalustre chez un enfant de 7 ans, Bull. et mém. Soc. méd. d. hôp. de Paris **53**:770, 1929.
15. Harvier, P., and Cattan, R., Purpura fulminans: Septicémie à D. Crassus, Bull. et mém. Soc. méd. d. hôp. de Paris **47**:611, 1931.
16. Fiorio, C., Ricerche sul significato patogeno di alcuni diplococchi Gram negativi, Gior. di batteriol. e immunol. **7**:523, 1931.
17. Lévy-Bruhl, M., Fréquence exceptionelle des suppurations otomastoidiennes à D. Crassus au cours de ces derniers mois, Ann. d'oto-laryng. **2**:1350, 1932.
18. Chevallier, P., Lévy-Bruhl, M., and Bernard, J., Contribution à la connaissance des infections attenuées à D. Crassus, Bull. et mém. Soc. méd. d. hôp. de Paris **48**:928, 1932.
19. Colombe, J., and Sauvage, F., Méningite Aigüe à D. Crassus, Arch. de méd. d. enf. **36**:420, 1933.
20. De Toni, G., and Gallerani, V., A proposito di un raro caso di pielocistite da pseudomeningococco (D. Crassus), Bull. d'Acad. med. Bologna **105**:133, 1933.
21. Dondi, G., Septicemia due to pseudomeningococcus (D. Crassus), Pediat. med. prat. **9**:230, 1934.
22. Sabatelli, F., Linfogranulomatosi maligna e infezione concomitante da D. Crassus, Minerva med. **1**:542, 1934.
23. Moreau, R., Langel, Fort, and Morel, Un cas mortel de septicémie à D. crassus avec endocardite, Bull. et mém. Soc. méd. d. hôp. de Paris **52**:1398, 1936.
24. Marcoff, K., Diplococchi gram negativi della flora tonsillare in condizioni normali e patologiche, Ann. laryng., otol. **12**:97, 1937.
25. Nasilowsky, A. D., Crassus causing purulent meningitis in nurslings: Two cases treated with benzyl sulfanilamide, Polska gaz. lek. **17**:478, 1938.
26. Bordes, L., Ceccaldi, J., Palinacci, A., and Berthon, J., Sur un cas de méningite mortelle à D. crassus observèe à Brazzaville, Bull. Soc. path. exot. **31**:357, 1938.
27. Chevrel, F., Deux nouveaux cas de méningite cerebrospinale à pseudo-meningocoques (D. Flavus I et D. Crassus) guéris par le traitement sulfamidé, Bull. et mém. Soc. méd. d. hôp. de Paris **56**:672, 1940.
28. Velu, H., Soulié, P., Courtade, R., and Gavandan, P., Diplococque de la souris; Infection pulmonaire et causes favorisantes, Compt. rend. Soc. de biol. **136**:371, 1942.

SPANISH ABSTRACT

Septicemia en un Prematuro Debida al Diplococcus Grassus

El D. grassus es un miembro de la familia Neisseria, siendo un habitante común, de poca virulencia, de la flora nasofaringea normal. Este organismo a veces puede asumir una virulencia marcada, encontrandose numerosos reportes en la literatura Europea de casos con meningitis y septicemias, asi como reportes aislados de pneumonia, otitis, mastoiditis, linfadenitis, abscesos cerebrales, amigdalitis, purpura y pielocistitis causadas por el D. grassus. Las caracteristicas bacteriologicas mas salientes de este organismo son la facultad de ser Gram-negativo y Gram-positivo y frecuentemente estas dos reacciones de coloración pueden demostrarse en los frotes hechos de una misma colonia.

Los autores reportan un caso de septicemia debida al D. grassus ocurrida en un prematuro, la cual se caracterizó por un comienzo agudo y participación marcada de los ganglios linfaticos. Este paciente fué tratado con quimoterapia combinada con resultados satisfactorios.

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SPIROMETRIC MEASUREMENTS OF LUNG FUNCTION IN HEALTHY CHILDREN

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Toronto

THE evaluation of pulmonary function in children is at present largely confined to clinical and radiographic methods of study. In adults the physiologic assessment of pulmonary function has assumed increasing importance since the initial work of Hutchinson[1] who, in 1846, by use of a closed circuit method, conducted the first carefully controlled study of vital capacity in 3000 adult subjects.

Subsequent work by numerous investigators was ably summarized by Myers[2] in 1925. In 1932, Christie[3] clarified the confusion of terms then applied to lung volume and its subdivisions. He also emphasized the advantages of graphic tracings in the measurement of lung volume and pointed out the unpredictable variations of such measurements among normal individuals and in the same individual. In 1933 and 1934, Hurtado and associates[4,5] carefully analysed the relative proportions of the various subdivisions of lung volume with respect to vital capacity and total lung volume. They were able to show that the wide variations among normal people could be consistently resolved by expressing the subdivisions of lung volume in terms of percentage of vital capacity or total lung volume. In 1939, the entire subject of spirography in pulmonary disease was reviewed by Cournand and associates[6] who added a description and evaluation of ventilation obtainable by this method. Subsequent publications by Cournand[7] and Eleanor deF. Baldwin and associates[8] have extended earlier observations on pulmonary ventilation in health and disease and have established the range of normal adult values.

Studies of vital capacity in children have been carried out by several investigators. Emerson and Green[9] in 1921 studied the vital capacity of 350 normal children and correlated this measurement with body surface. Edwards and Wilson[10] in 1922 made similar observations in 362 normal children and found a close correlation between vital capacity and standing height. In the same year Stewart[11] published statistical data on the vital capacities of some 2700 children and compiled excellent tables relating this function to sex, age, standing and sitting height, and weight. Since that time other investigators, Stewart and associates,[12,13] B. T. Baldwin[14] and Püschell,[15] have made observations on single phases of pulmonary function limited for the most part to studies of lung volume.

With the rapidly advancing technics of medical and surgical management of pulmonary disease a more comprehensive evaluation of pulmonary function in children is needed in order to judge the degree of impairment of function and the efficacy of treatment. Some of the methods of study already developed in adults may be applied to children. The purpose of this investigation is to assess the results of such methods in a group of normal children using a closed circuit or rebreathing apparatus.

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Methods and Material

A group of 50 children ranging in age from 5¾ yr. to 14 yr. was selected for study. Of these 13 were from 5 to 8 yr., 18 from 8 to 10 yr., 9 from 10 to 12 yr., and 10 from 12 to 14 yr. The mean age of the group was 9.4 yr., 30 were males and 20 were females. Thirty-seven children in good health, with no history of cardiac or pulmonary disease, were studied at Baltimore Children's Home. Thirteen children were studied at Happy Hills Convalescent Home in Baltimore. The latter subjects were fully active following convalescence for diseases not affecting heart or lungs, and were about to be discharged.

The following measurements were made on each child:

1. Volume of resting ventilation/min.
2. Rate of oxygen consumption/min. at rest.
3. Vital capacity and its subdivisions, in the supine position.
4. Maximum voluntary ventilatory capacity in the standing position.

Definitions and Nomenclature

Tidal air is the volume of a single inspiration (tidal inspiration) or expiration (tidal expiration). Since this volume may vary widely even in steady physiologic states, only an average figure for a

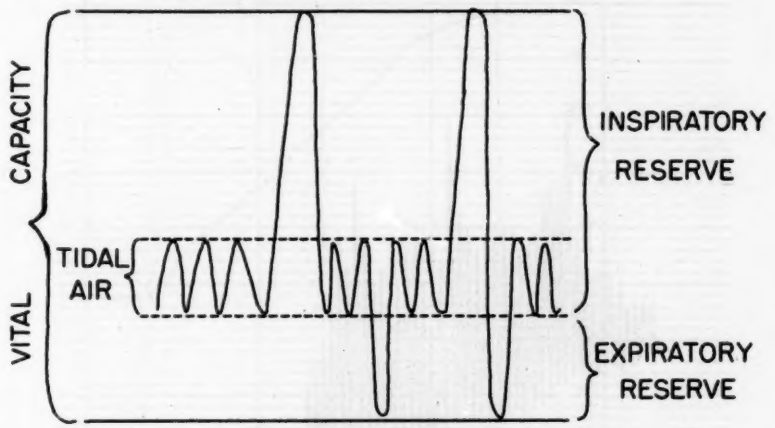

Chart 1. Subdivisions of vital capacity.

given state has any real meaning. In conformity with Christie and others, the present investigators have employed the resting respiratory level as the most consistent point of reference from which to measure the subdivisions of vital capacity. This resting respiratory level is considered to be the level at which the resting tidal expiration ceases and the succeeding tidal inspiration commences.

At the suggestion of J. H. Comroe, Jr.,[16] the terms complemental and supplemental or reserve air were replaced by the terms inspiratory reserve and expiratory reserve. The inspiratory reserve is the maximum volume of air that can be voluntarily inspired from the resting respiratory level, and includes the tidal air by this definition: The expiratory reserve is the maximum volume of air that can be voluntarily expired from the resting respiratory level and does not include tidal air (chart 1).

The vital capacity is the largest volume of air that can be expired following a maximum inspiration, or vice versa.

Minute volume is the volume of ventilation in l./min.

The term maximum voluntary ventilatory capacity is applied to what is more generally known as the maximum breathing capacity because of its self-explanatory wording and in order to distinguish it from the maximum ventilations secondary to either exercise or chemical stimulation.

Breathing reserve is the term applied to the volume obtained by subtracting the minute volume

from the maximum voluntary ventilatory capacity and is usually converted from l./min. to per cent of maximum voluntary ventilatory capacity.

Apparatus

The apparatus employed was the Benedict-Roth closed circuit wet spirometer fitted with a kymograph and Reichert[17] ventilometer.* The volume of ventilation was obtained by measurement of the

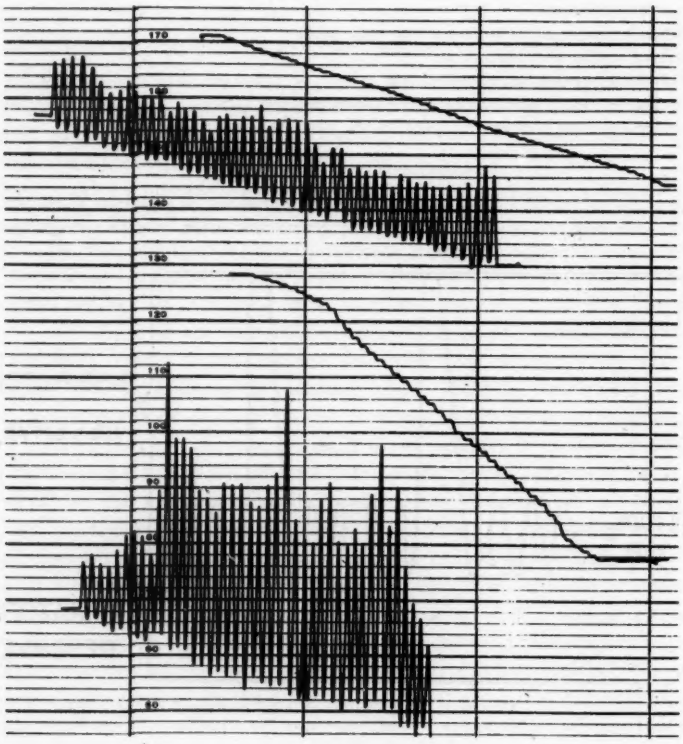

Chart 2. Consecutive tracings of resting ventilation on same child. Initial tracing is below and exhibits marked hyperventilation due to apprehension in contrast to second attempt. Stepwise tracing in each instance is ventilometer record of cumulative inspired volume. Distance between each vertical line on kymograph paper represents time interval of 1 min. Distance between heavy horizontal lines is equal to 1 cm. and represents volume of 210 ml. These calibrations are same for all subsequent tracings (charts 3-6).

ventilometer tracing. Rate of oxygen consumption was measured by the upward slope of the tracing of tidal ventilation with a soda lime canister in the expiratory side of the closed circuit to absorb carbon dioxide. Measurement of the vital capacity and its subdivisions and of maximum voluntary ventilatory capacity were made from the tracings obtained with the soda lime canister removed from the circuit. A rubber mouth piece and nose clip were used, rather than a face mask, to reduce apprehension and to minimize leakage.

* Manufactured by Warren E. Collins, Inc., Boston.

PROCEDURE

Children were brought into a quiet room, one at a time, and allowed to examine the apparatus. The function of the mouth piece was explained and the child was allowed to fit it in the mouth before it was attached to the apparatus. The nose clip was similarly presented and examined. The child was then allowed to recline on a bed for a full 3 min., breathing room air through a valve after the mouth piece was connected to the apparatus. By this means initial anxiety was allayed in most cases. Before the actual test was performed the mouth piece and nose clip were removed and the child was questioned regarding his comfort and reassured as to the ease of the test. Following reinsertion of the mouth piece and reapplication of the nose clip, tests for resting ventilation and oxygen consumption were performed casually and quietly. At least 3 resting ventilation tracings

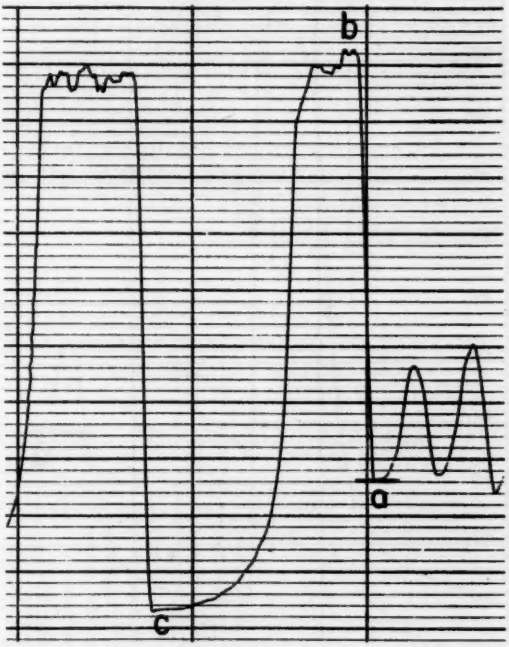

CHART 3. Inspiratory reserve tracing of 11 yr. old child. "ab" represents maximum inspiration. "bc," subsequent maximum expiration representing vital capacity.

were taken and in most instances 4 were required before this portion of the study was concluded. The importance of repeated tracings is illustrated in chart 2. It was found that closing of the eyes, reading or listening to a conversation interrupted the even breathing of the subject. For this reason the child was allowed to keep his eyes open but was asked not to watch the rise and fall of the spirometer bell. At the conclusion of this portion of the study, the nose clip and mouth piece were removed, the child was complimented on his cooperation and questioned regarding the ease of the performance.

Lung volume studies were explained to the subject in the nature of a game and a competitive element was introduced by citing the good results of the preceding child. Following the removal of the soda lime canister and flutter valve, the apparatus was reassembled and the child was allowed to practice maximum inspiratory and expiratory efforts through the mouth piece before it was connected to the system. The test was performed with the child in a reclining position, the head being elevated from 25 to 30 cm. above the feet. Encouragement was given throughout this trial. Inspiratory

reserve tracings were taken initially. These were obtained by having the child inspire maximally from a resting level followed by a maximum expiratory effort (chart 3). At least 3 such efforts were recorded. Similarly 3 expiratory reserve tracings were obtained by having the child expire maximally from a resting level followed by a maximum inspiration (chart 4). The best inspiratory and expiratory efforts were taken for inspiratory and expiratory reserve figures and the best single tracing was measured for vital capacity.

The final measurement was that of standing maximum voluntary ventilatory capacity. Once again this procedure was explained and the child allowed to practice before the records were taken. Four

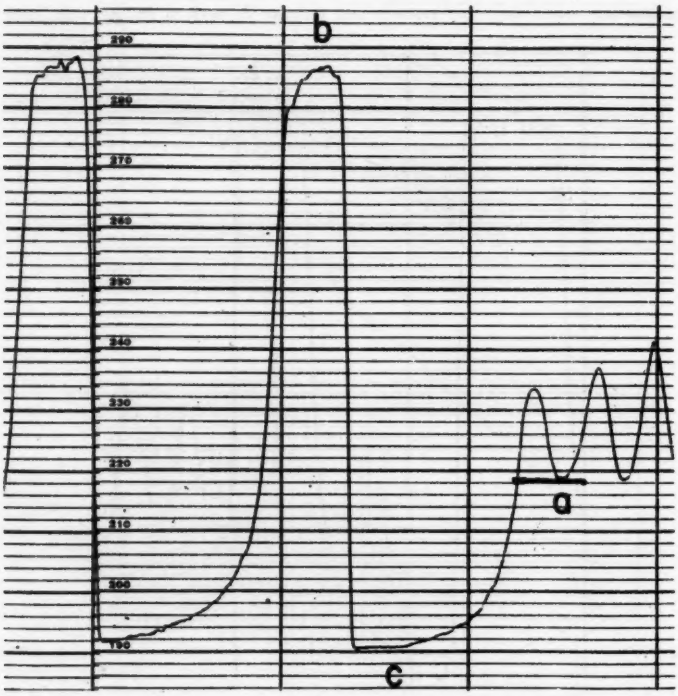

CHART 4. Expiratory reserve tracing with same subject as chart 3. "ac" represents maximum expiratory effort. "cb," subsequent maximum inspiration representing vital capacity.

such tracings were recorded by means of rapid deep respirations, 2 with emphasis on rapidity and 2 with emphasis on depth of respiration. Examples of the 2 types of tracings obtained are seen in charts 5 and 6. As before, a spirit of competition was engendered by comparison with preceding children.

A full 30 min. was necessary for a complete record on each child under 10 yr. of age. A somewhat shorter period was necessary for children from 10 to 14 yr. Calculations of lung volume and average tidal air were corrected to 37° saturated (body temperature at prevailing barometric pressure, saturated with water vapour), the remaining calculations were corrected to standard temperature and pressure, dry (S.T.P.D.).

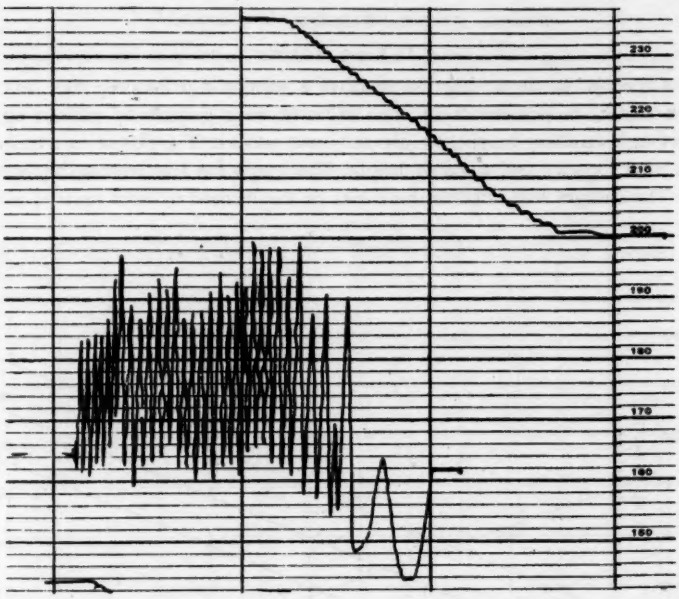

CHART 5. Example of maximum voluntary ventilatory capacity with emphasis on rapidity of breathing. MVVC = 60.0 l./min. S.T.P.D.

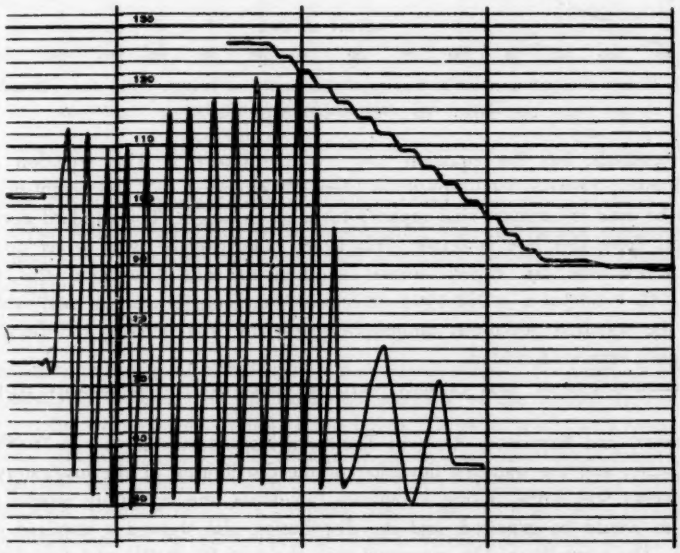

CHART 6. Example of maximum voluntary ventilatory capacity (same subject as chart 5) with emphasis on depth of breathing. MVVC = 58.1 l./min. S.T.P.D.

Results

1. Lung Volume

Vital Capacity: In an attempt to establish a relationship between this function and a known factor, measurements of vital capacity were graphically plotted against the factors of age, standing height, weight and body surface. The closest correlation existed between vital capacity and standing height. The graph for this relationship is shown in chart 7. The straight line fitted to these data by the method of least squares, minimizing

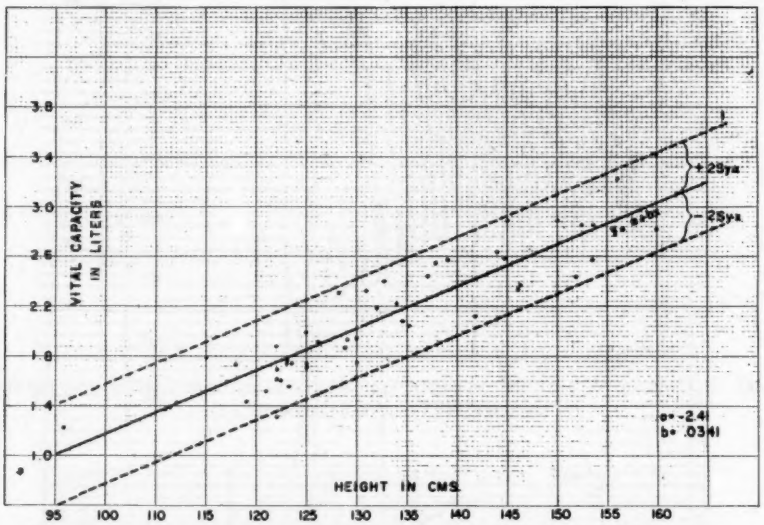

CHART 7. Graph illustrating relationship of vital capacity to height. Solid line represents mean. Dotted lines represent range about mean.

vertical residuals, has the equation $y = -2.41 + 0.0341\,x$. This equation describes the relationship between vital capacity in liters 37° saturated (y), and height in cm. (x), and can be used to estimate vital capacity for a given height. The standard deviation of the points from this line is 0.199. This latter value may be used to set up a range within which one can expect normal children to fall. Therefore, this range is $y = -2.41 + 0.0341\,x \pm 2(0.199)$. In Stewart's large series relating vital capacity and height, the standard deviations ranged from .140 to .413 in boys and from .146 to .332 in girls, expressed in liters.

The subdivisions of vital capacity were calculated with vital capacity representing 100%.

Inspiratory and Expiratory Reserve: The mean inspiratory reserve was 76.0% of the vital capacity, and the standard deviation of the distribution of the inspiratory reserve measurements was 4.6%. Using a separate calculation the expiratory reserve averaged 24.0%, as would be expected, and the distribution also showed a standard deviation of 4.6%. These results may be compared with those of Püschell[15] who found the mean inspiratory reserve to be 77.4% in males and 79.72% in females, and the mean expiratory reserve to be 22.6% in males and 20.28% in females.

2. Maximum Voluntary Ventilatory Capacity

This measurement was also plotted against factors of age, standing height, weight and body surface. As with vital capacity this determination showed the closest correlation to standing height. The graph illustrating this relationship is shown in chart 8. Using the same procedures as were used with vital capacity, the estimated range of normal maximum voluntary ventilatory capacity for a known standing height is $y = -39.001 + 0.7712\ x \pm 2(8.077)$, where y = maximum voluntary ventilatory capacity in l./min., and x = standing height in cm. Maximum voluntary ventilatory capacity was also plotted against vital capacity which again revealed a linear

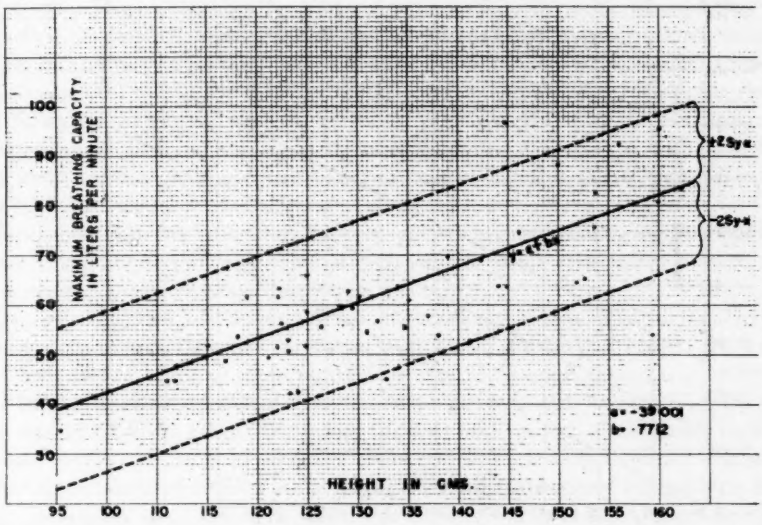

CHART 8. Graph to illustrate relationship between maximum voluntary ventilatory capacity and height.

relationship (chart 9). Since maximum voluntary ventilatory capacity depends in part on vital capacity this relationship would be expected. For purposes of prediction, however, it would be preferable to use a more accurately determined standard such as standing height.

3. Resting Ventilation

This measurement was calculated in l./min./m² body surface. No adequate correlation was demonstrable between this determination and any of the known factors of age, standing height, etc. For the children studied here the mean was 5.94 l./min./m² and the standard deviation was 1.64. It should be pointed out that the distribution curve of this variable was asymmetric with a few too many instances of high value due to hyperventilation. Baldwin et al.,[8] in studying adults from 16 to 34 years of age, found the mean ventilation to be 3.6 l./min./m² with a standard deviation of 0.3 in males and 3.2 l./min./m² with a standard deviation of 0.4 in females.

4. Breathing Reserve

As mentioned previously, this measurement is the result of the difference between maximum voluntary ventilatory capacity and resting ventilation expressed as per cent of maximum voluntary ventilatory capacity. Because of the variability of resting ventilation, the distribution of results of this determination also showed some asymmetry. No correlation existed between these figures and any of the known standards. The mean breathing reserve of the group was 89.7% with a standard deviation about the mean of 3.4. In a group of 54 adults where no dyspnea was felt during the recovery period

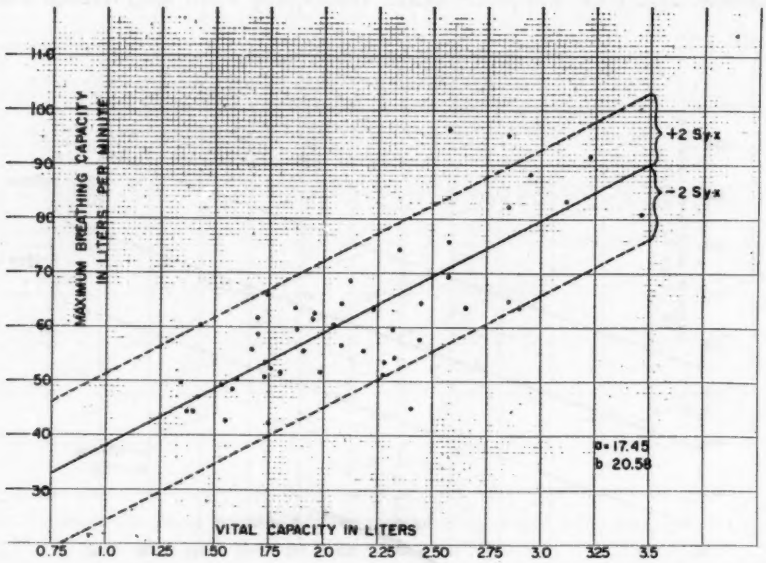

CHART 9. Graph illustrating correlation between maximum voluntary ventilatory capacity and vital capacity.

from a standard exercise test, Cournand and Richards[7] found the average breathing reserve to be 91.7% of maximum voluntary ventilatory capacity with a standard deviation of 2.4

5. Average Tidal Air

Although there was a tendency for this measurement to vary according to age, the correlation was slight. The mean tidal air was 388 ml. and the standard deviation was 96.62.

6. Oxygen Consumption

In each instance oxygen consumption was calculated in ml./m² body surface. Again there was no adequate correlation between these results and the standards of age, standing height, etc. The distribution of the results revealed the mean oxygen consumption to be 174.64 ml./min./m² and the standard deviation of the distribution was 39.20. The

mean value of 174.64 ml./min./m² when converted to calories/m²/hr. closely approximates DuBois' standard[18] of basal metabolism for a 9 year old male subject. In Baldwin's[8] study the mean oxygen consumption of adult males in the age group of 16 to 34 years was 146 ml./min./m², with a standard deviation of 14. In females of the same age group the mean oxygen consumption was 126 ml./min./m² with a standard deviation of 10.

Discussion

The major problem in determinations of this sort in children is the variability produced by apprehension, unfamiliarity with the apparatus and possible limitation in cooperation. Steps were taken, as discussed previously, to overcome some of these undesirable influences. In most instances the children gave what appeared to be maximal efforts and for this reason the values obtained for vital capacity and maximum voluntary ventilatory capacity are not distorted by these influences. However, values for resting ventilation and oxygen consumption are more liable to variations from these causes.

The linear relationship between vital capacity and height seems well established from this study and has previously been found to exist by Edwards and Wilson,[10] Stewart[11] and B. T. Baldwin.[14]

Maximum voluntary ventilatory capacity plotted against standing height showed a linear relationship which, while not as well defined as the relationship between vital capacity and standing height, is clearly apparent.

The measurements of resting ventilation, breathing reserve, tidal air and oxygen consumption showed no useful correlation with known standards of height, age, weight and body surface. Each of these functions is affected by apprehension and excitement and because of this the standard deviation of the group in each instance is greater than that seen in the adult group. No attempt has been made in such a small study to obtain separate results for males and females. There seemed to be little difference due to sex either in the scatter of subjects in the graphs or in the distributional relationships. However, in previous large studies in which vital capacity was determined, males have been shown to have a slightly greater vital capacity throughout.

Summary and Conclusion

A group of 50 normal children between the ages of 5¾ and 14 years has been studied by means of gross spirometry in an attempt to derive base line results for comparison with patients suffering from pulmonary disease. The results of these studies are summarized below:

1. The normal range of vital capacity for a given height is estimated on the basis of these observations to be given by the equation $y = -2.41 + 0.0341\ x \pm 2(0.199)$, where y = vital capacity in liters, and x = standing height in cm.

The subdivisions of vital capacity are expressed in terms of per cent of vital capacity. For this group the average inspiratory reserve was 76.0% and the standard deviation of the distribution was 4.6%. Correspondingly, the average expiratory reserve was 24.0%, and the standard deviation was 4.6%.

2. The normal range of maximum voluntary ventilatory capacity is estimated as $y = -39.001 + 0.7712\ x \pm 2(8.077)$, where y = maximum voluntary ventilatory capacity in l./min. and x = standing height in cm.

3. The average breathing reserve in the group studied was 89.7%, and the standard deviation 3.4%.

These studies compared favorably with those observed by other investigators.

4. The results of resting ventilation, average tidal air and oxygen consumption revealed more variation than similar studies in adults as illustrated by wider standard deviations. This variability would be expected in view of the apprehension and excitability of young children. The mean resting ventilation for the group studied was 5.94 l./min./m^2 with a standard deviation of 1.64. The mean oxygen consumption was 174.64 ml./min./m^2 and the standard deviation was 39.20.

The group studied was a relatively small one and the results must thus be subject to review as more data on pulmonary function in children becomes available.

Acknowledgment

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References

1. Hutchinson, J., On capacity of lungs and on respiratory movements with view of establishing precise and easy method of detecting disease by spirometer, Lancet **1**:630, 1846.
2. Myers, J. A., Vital Capacity of Lungs, Monograph, Baltimore, Williams & Wilkins Company, 1925.
3. Christie, R. V., Lung volume and its subdivisions. I. Methods of measurement, J. Clin. Investigation **11**:1099, 1932.
4. Hurtado, A., and Boller, C. J., Studies of total pulmonary capacity and its subdivisions. I. Normal absolute and relative values, J. Clin. Investigation **12**:793, 1933.
5. Hurtado, A., Fray, W. W., Kaltreider, N. L., and Brooks, W. O. W., Studies of total pulmonary capacity and its subdivisions. V. Normal values in female subjects, J. Clin. Investigation **13**:169, 1934.
6. Cournand, A., Richards, D. W., Jr., and Darling, R. C., Graphic tracings of respiration in study of pulmonary disease, Am. Rev. Tuberç. **40**:487, 1939.
7. Cournand, A., and Richards, D. W., Jr., Pulmonary insufficiency. I. Discussion of physiological classification and presentation of clinical tests, Am. Rev. Tuberc. **44**:26, 1941.
8. Baldwin, Eleanor deF., Cournand, A., and Richards, D. W., Jr., Pulmonary insufficiency. I. Physiological classification, clinical methods of analysis, standard values in normal subjects, Medicine **27**:243, 1948.
9. Emerson, P. W., and Green, H., Vital capacity of lungs of children, Am. J. Dis. Child. **22**:202, 1921.
10. Edwards, D. J., and Wilson, M. G., Analysis of some factors of variability in vital capacity measurements of children, Arch. Int. Med. **30**:638, 1922.
11. Stewart, C. A., Vital capacity of lungs in children in health and disease, Am. J. Dis. Child. **24**:451, 1922.
12. Stewart, C. A., and Platou, E. S., Lungs in infancy and childhood, Minnesota Med. **8**:715, 1925.
13. Stewart, C. A., Consideration of extent of normal variability of vital capacity of lungs of children, Am. Rev. Tuberc. **13**:272, 1926.
14. Baldwin, B. T., Breathing capacity according to height and age of American born boys and girls of school age, Am. J. Phys. Anthrop. **12**:257, 1928.
15. Püschell, E., Die Lungenvolumina gesunder Kinder, Monatschr. f. Kinderh. **63**:450, 1935.
16. Comroe, J. H., Jr., Personal communication to the authors.
17. Reichert, P., Oxygen utilization as index of respiratory efficiency: Clinical device for its determination, J. Aviation Med. **7**:63, 1936.
18. Boothby, W. M., and Sandiford, Irene, Normal values of basal or standard metabolism: Modification of DuBois standards, Am. J. Physiol. **90**:290, 1929.

SPANISH ABSTRACT

Medida Espirometrica de la Funcion Pulmonar de Niños Saludables

Un grupo de 50 niños normales entre cinco y catorce años de edad fueron estudiados espirometricamente para asi obtener un promedio basal optimo que sirva de comparacion con pacientes sufriendo de enfermedad pulmonar. Los resultados de estos estudios se sumarizan a continuacion:

1.—Los limites normales de la capacidad vital (conociendo la talla) es determinada de acuerdo con este estudio mediante la equación $y = -2.41 + 0.0341 \times \pm 2(0.199)$, siendo y = capacidad vital en litros y x = talla en centimetros.

Las subdivisiones de la capacidad vital es expresada en porciento de capacidad vital. Para este grupo el promedio de reserva inspiratoria fue de 76.0% y la "standard deviation" de la distribucion fué 4.6%. Correspondientemente el promedio de reserva expiratoria fué de 24.0% y la "standard deviation" fue 4.6%.

2.—Los limites normales de la capacidad ventilatoria voluntaria maxima es establecido mediante $y = -39.001 + 0.7712 \times \pm 2(8.077)$, siendo y = capacidad ventilatoria voluntaria maxima en l./min. y x = talla en centimetros.

3.—El promedio de reserva respiratoria en el grupo estudiado fué 89.7% y la "standard deviation" 3.4%.

Estos resultados son comparables a los obtenidos por otros investigadores.

4.—Los résultados de la ventilación en reposo, el promedio de aire tidal, y el consume de oxigeno fueron mas variables que los estudios similares realizados en adultos. Estas variaciones eran de esperarse debido a la mayor aprension y excitabilidad de los niños. El promedio de la ventilacion en reposo para el grupo estudiado fue 5.94 l./min/m2 y la "standard deviation" 1.64. El promedio de consume de oxigeno fue 174.64 ml/min/m^2 y la "standard deviation" fue 39.20.

Los autores estiman que el grupo estudiado fué relativamente pequeño y los resultados deben sujetarse a una revisión tan pronto como mas data sobre la funcion pulmonar de niños es obtenida.

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VITAMIN A POISONING

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ALTHOUGH the effects of excessive amounts of vitamin A on animals have been studied for many years, only recently have similar effects from high doses of the vitamin been noted in man. A survey of the literature reveals records of only 14 cases, all in infants and children, who exhibited symptoms of a syndrome due to overdosage with vitamin A.

This paper presents two examples of this syndrome. The data indicate that excess intake of vitamin A causes saturation of the tissues which leads to local toxic changes. Finally, differential diagnostic criteria are discussed in the attempt to make easier the recognition of the condition.

HISTORICAL

During the late 1920's and early 1930's, the first reports of toxic effects of excess vitamin A on animals appeared. Von Drigalski[1] administered 0.5 and 1.0 cc. of a vitamin concentrate "Vogan" (containing 40,000 rat units of vitamin A/cc.) to white rats daily. Within 4 to 6 days these animals showed dishevelled fur, marked emaciation and loss of weight. After 5 to 8 days, catarrhal symptoms such as conjunctivitis, hemorrhagic rhinitis, and diarrhea appeared, and within 5 to 19 days, the animals on both dosages died. Examination of these animals disclosed a variety of lesions in the kidneys, spleen, heart, muscle, testes and liver.

At the same time Collazo and Rodriguez[2] conducted similar experiments with rats. In addition to trophic changes of the skin and loss of hair, they noted inflammatory changes of the eyes, bilateral exophthalmos, cessation of growth and spontaneous fractures of bones. When the overdosage was stopped the animals recovered and gained weight. Similar changes were found by Finucci,[3] Vedder and Rosenberg,[4] and Chalier and Jeune[5] in guinea pigs and other animals.

Another group of investigators, led by Russo,[6] was unable to duplicate these effects in animals; they concluded that high doses of vitamin A were not toxic. Clausen,[7] in an excellent review of the experimental work on the subject, came to the conclusion that "the literature was so contradictory at that time (1938) as to afford no evidence that vitamin A would have a harmful effect on human beings."

Josephs[8] in 1944 reported the first case of hypervitaminosis A in a child. His report was followed by those of Toomey and Morissette,[9] Rothman and Leon,[10] Dickey and Bradley,[11] Fried and Grand[12] and Caffey.[13] In the accompanying tables (1 and 2) are recorded the symptoms, physical findings and laboratory data of these cases.

The data in these cases indicate that hypervitaminosis A produces a characteristic clinical syndrome. Table 2 is a tabulation of the outstanding signs and symptoms.

From the Pediatric Service, The Jewish Hospital of Brooklyn, Brooklyn.

Presented in part at a meeting of the Brooklyn Academy of Pediatrics, Brooklyn, April 26, 1950, and in part at the Twenty-Third Graduate Fortnight of the New York Academy of Medicine, Oct. 18, 1950.

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The authors have recently observed a child in whom the diagnosis of hypervitaminosis A was established by laboratory studies. The clinical features of a second case, seen earlier but not recognized, were so characteristic as to make such a diagnosis highly probable.

Case Reports

Case 1: J.L., a 2½ yr. old white boy, complained of painful extremities for 2 wk.

Two months before, the child became less active and preferred not to walk. One month earlier a pruritic rash developed on his buttocks, back and abdomen; at the same time fissures appeared on the lips and sores in the corners of the mouth. The skin eruption improved spontaneously, but despite gentian violet therapy, the fissuring and soreness of the lips remained. Ten days later his mother noted that the child would cry whenever he was handled and his right leg was especially tender to the touch. Two weeks before admission the child began to limp on his right leg. One and a half weeks before the child complained of pain in the right forearm. Two days after this the left forearm became painful. A roentgenogram revealed periosteal elevation of the proximal portion of the right tibia and the left ulna. During the next few days he remained in bed and was very irritable.

It was learned that during the first year of life the child received 10 drops of oleum percomorphum®* daily. He was also given orange juice which was frequently refused and for which 0.6 cc. of vifort®† were substituted. At 1 yr. the oleum percomorphum was discontinued and infadol®,‡ 1 teaspoonful a day, was given. From 1½ yr. of age, the child took 1-1½ oz. of orange juice daily. For the last few months he received 2 teaspoonsful of a vitamin B preparation. The total vitamin A and D intake for the past 1½ yr. was estimated to be much more than 100,000 U.S.P. u. of vitamin A and 20,000 U.S.P. u. of vitamin D daily.

Physical examination revealed an irritable, thin child with slight bony protuberances over both temporal areas (the mother stated these had become manifest in the past month). The child lay immobile in bed and appeared chronically ill. Other positive findings included: fissuring of the lips, coarse sparse hair on the head, the liver extending 1 finger below costal margin, meatitis, and painful extremities. The latter, although extremely tender to the touch, presented no redness or heat but there was a definite slight swelling at the anterior aspect of the right tibia.

The differential diagnoses on admission included scurvy, leukemia and neuroblastoma.

Laboratory data: Several specimens of urine were normal. The hemoglobin was 70% (Haden-Hauser) and RBC was 3.8 million/cmm.; WBC was 10.8 thousand/cmm., with a normal differential. Adequate platelets were seen on smear and the reticulocyte count was 0.4%. Bleeding time was 1 min., 15 sec., and the clotting time was 3 min., 12 sec. Tuberculin and Mazzini tests were negative. The sedimentation rate was 13 mm. after 1 hr. Serum calcium was 11.5 mg. %; serum phosphorus 2.9 mg. % and serum alkaline phosphatase activity 12 Bodansky u. Total serum protein was 6 gm. %; albumin 4.5 gm. % and globulin 2.3 gm. %. Blood sugar was 119 mg. % and the blood urea N was 13 mg. %. Serum cholesterol was 241 mg. % with a free cholesterol of 56 mg. % (23.2%). Total lipids were 714 mg. %. Cephalin flocculation was 0. Thymol turbidity was 2.2 MacLaglen u. while the prothrombin time was 14.1 sec. (control 12.1 sec.) and bilirubin by the van den Bergh method was 0.5 mg. %. A vitamin C loading test showed an excretion of 66% of the ingested vitamin C in the urine (normal: at least 40%) and there was a positive Sulkowitch test for calcium in the urine.

Because a general vitamin survey was undertaken a vitamin A level in the blood was determined. This was found to be 837 µg. %¶ while the carotene value was 223 µg %. It was the findings of this extremely high vitamin A level that established the diagnosis of hypervitaminosis A. The vitamin A level was redetermined 2 days later and was found to be 695 µg % of which 67.3% proved to be in the alcoholic form.

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* Oleum Percomorphum (Mead Johnson) is composed of the liver oils of percomorph fishes with viosterol and other fish liver oils. It contains 60,000 u. vitamin A and 8,500 u. vitamin D per gram.

† Vifort (Endo Products) is a water dispersible polyvitamin preparation. Each 0.6 cc. contains 5,000 u. vitamin A and 1,200 u. vitamin D in addition to vitamins of the B complex group.

‡ Infadol (I.V.C.) is a vitamin A and D concentrate. Each 3 drops contain 5,000 u. vitamin A and 1,000 u. vitamin D.

¶ One microgram of vitamin A is equivalent to 3.57 U.S.P. u.

TABLE 1

Cases of Hypervitaminosis A Previously Reported

Case No.	Author	Age	Symptoms	Vitamin A Amount and Approx. Units (According to authors)	Physical Examination	Plasma Vit. A. level	Serum			RG findings	Course after discontinuing vitamin
							Ca mg./100 cc.	P mg./100 cc.	Alkaline Phosphatase Bodansky units		
1	Josephs 1944	3 yr.	Diminished appetite and disinclination to play for 18 mo. Hepatosplenomegaly. Increasing anemia. Hair sparse and coarse.	Since age of 2–3 mo., 1 tsp. halibut liver oil daily (240,000 U.S.P. u. q.d.).	Hair sparse, dry and coarse. Slight clubbing fingers and toes. Hepatosplenomegaly.	910 U.S.P. u.	10.1	4.5	19.3	Thin cortex and vacuolated medullary cavities in phalanges and metacarpals. Epiphyses of upper ends of humeri and tibiae were mottled.	Within 2 mo., appetite improved, gained weight, hair began to grow back.
2	Toomey and Morissette 1947	23 mo.	Intermittent swelling and tenderness of forearms and lower extremities for 6 mo. Irritability and anorexia. Constipation and pruritis. Abnormal craving for butter.	1–2 tsp. of cod liver oil daily plus 1–2 tsp. of Oleum Percomorph daily since newborn period (250,000–500,000 u.).	Hair sparse, coarse and dry. Lips dry and cracked. Tenderness over femur, both radii and tibiae.	700 I.U.	11	4.5	.62 mg.	Periosteal line on right femur and left tibia. Pronounced periosteal thickening of ulnae. Broad growth lines at ends of all long bones.	Within 8 days periosteal pain and tenderness disappeared.
3	Rothman and Leon 1948	14 mo.	Pruritis, irritability and anorexia for 9 mo. Wrist pain for 5 mo. Loss of hair for 2 mo. Fissuring of lips. Yellow tinge to skin.	Oleum Percomorph since 3–4 wk. of age. 9 mo. receiving 1 tsp. daily. At 6 mo., 10 gtts. Vifort added (130,000 units).	Sparse hair. Lips cracked. Inability to stand.	2,081 I.U.	7.6	4.1	11.9	Periosteal reaction on both clavicles and ulnae.	Within 24 hr. child stood and physical activity increased. Bone tenderness disappeared. Appetite better and irritability less marked.
4	Rothman and Leon 1948	22 mo.	Painful extremities, difficulty in walking and irritability for 18 mo. Erythematous rash and pruritis on trunk.	O.P.* since 1 mo. At 10 mo. 12–20 gtts/day plus 250,000 units Squibbs Vit. A. At 16 mo. 20–25 gtts. O.P.*/day and 50–100,000 units Squibbs Vit A. (total 100–200,000 units).	Hair fine, dry and coarse. Lips dry and cracked. Pruritic marks on trunk. Hepatomegaly.	600 I.U.	12	5	8	Periosteal proliferation of ulnae and left clavicle	Within 1 wk. pain in extremities and bone tenderness disappeared. By 1 mo. symptoms had subsided.
5	Dickey and Bradley 1948	22 mo.	Pruritis, painful upper extremities for 4 mo. Swelling on scalp for 6 wk. Restlessness.	Since newborn period 3 tsp. Navitol and large amounts of C.L.O. plus 10 gtts. ViPenta. Also large amts. of butter. (Total 400,000 units for 1½ years).	Thin, coarse hair. Pruritic areas over legs and trunk. Hepatomegaly. Tenderness of left forearm, right arm and left leg.	943 I.U.	10.2	5	17	Periosteal elevation in bones of forearm.	Within few days, began to improve, stopped limping. Swellings in arms reduced. Appetite improved.
6	Fried and Grand 1950	16 mo.	Pruritis and irritability 10 mo. Anorexia, severe tenderness of upper and lower extremities for 10 days.	Since 2 wk. of age 30 gtts. O.P.* q.d. Gradually increased in a few months to 2 tsp. q.d. (500,000 u.).	Tenderness and swelling of upper extremities. Tender lower extremities. Pruritic marks over body. Hepatomegaly.	1,630 I.U.	10.3	4.6	35	Subperiosteal elevations of ulnae.	Improvement within days.
7	Fried and Grand 1950	24 mo.	Pruritis, tenderness of upper and lower extremities for 2 mo. Irritability, anorexia and loss of weight.	½–¾ tsp. of O.P.* q.d. (120–18,000 u.). ½–¾ lb. of butter at sitting.	Sparse, coarse hair. Pruritic marks over body. Tender extremities. Hepatomegaly.	700 I.U. 1,600 I.U.	10.4	4.8	26	Subperiosteal elevations of both ulnae and both tibiae.	Slowly made complete recovery.

TABLE 1—(*continued*)

Case No.	Author	Age	Symptoms	Vitamin A Amount and Approx. Units (According to authors)	Physical Examination	Plasma Vit. A. level	Serum			RG findings	Course after discontinuing vitamin
							Ca mg./100 cc.	P mg./100 cc.	Alkaline Phosphatase Bodansky units		
8	Caffey 1950	25 mo.	Fatiguability and anorexia for 6 mo. Left shank and foot swollen for 4 mo.	150,000 u. vitamin A for several mos. q.d.	Dry, cracked lips. Bilateral clavicular swelling, swelling of anterior left tibia.		10.6	4.3	18	Cortical hyperostoses of both clavicle, right and left 7th ribs, right femur, left tibia, right fibula, all save 1st metatarsals.	Discharged in 22 days from hospital asymptomatic.
9	Caffey 1950	21 mo.	Tender lump on right shin for 2 mo. Unwilling to walk. Irritable. Anorexia for 3 wk. Tender swellings on left forearm and dorsum right foot for 2 wk.	1 tsp. O.P.* q.d. for 9 mo. (250,000 u.).	Lips cracked. Tender swellings in occiput, both forearms, ventral surface right shank, lateral aspects of dorsum both feet.	330 u.				Multiple cortical hyperostoses on both ulnae, left tibia and both 5th metatarsals.	Asymptomatic 4 days.
10	Caffey 1950	12 mo.	Soreness of left shoulder and swelling and failure to use left arm for 3 wk.	2 tsp. O.P.* q.d. for 6 mo. (500,000 u.)	Pruritic areas on body. Left forearm had firm tender swelling.	1,384 I.U.	9.9	4.8	19	Bilateral cortical hyperostoses of ulnae.	Asymptomatic in 4 days.
11	Caffey 1950	32 mo.	Painful feet for 3 wk. Tender swellings of left hand, left arm, left shin. Irritability.	1 tsp. of O.P.* q.d. for 15 mo. (250,000 u.)	Hard tender swellings over left ulna, left thumb, 2nd left metacarpal and left tibia.		10.7	4.9	19	Cortical hyperostoses 2nd left metacarpal, both ulnae, both tibiae and fibulae, and both 4th metatarsals.	Hospital course uneventful.
12	Caffey 1950	18½ mo.	Pain in bones for few wk. Appetite always poor. Irritable.	After 12th mo. ½–¾ tsp. of Drisdol (Vit. A). After 13th mo. 1 tsp. Drisdol (Vit. A) q.d. (250,000 u.).	Both hands, left shank and both forearms were swollen and tender. Hepatomegaly.	1,395 u.	10.5	3.6	9.7	Cortical hyperostoses of both clavicles. 6th and 7th right ribs, both ulnae, right radius, left tibia, right fibula, 4th and 5th right metatarsals, both 4th metacarpals.	Clinical recovery rapid.
13	Caffey 1950	24 mo.	Pain, tenderness and swellings of extremities for 2 mo.	100,000 u. q.d. for 7 mo. prior to admission.	When seen by author 2 mo. after onset no positive physical findings.					Cortical thickenings both ulnae and 5th metatarsal.	Recovery.
14	Caffey 1950	37 mo.	Pruritic rash for 5 mo. Arms and legs tender for 2 mo.	1 tsp. of Navitol q.d. for 17 mo. (200,000 u.)	Skin has many scratch marks. Hepatomegaly. Tender extremities.		10.8	5.2	22	Cortical hyperostoses of both clavicles and ulnae.	Rapid recovery.

* Oleum Percomorphum.

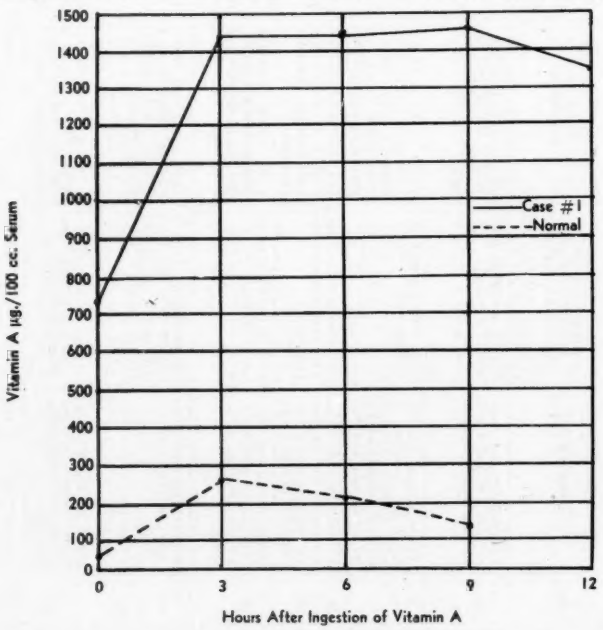
TABLE 2

FREQUENCY OF SIGNS, SYMPTOMS AND LABORATORY FINDINGS IN 16 REPORTED CASES OF HYPERVITAMINOSIS A
(Includes 2 cases in this report)

Signs, symptoms and laboratory data	No. of cases
Onset after 6 mo. of age	16
Cortical thickening of bones (seen on RG)	16
Normal serum Ca and P	14 (recorded in only 14 cases)
Painful swellings in extremities	13
Irritability	12
Pruritus	10
Increased alkaline phosphatase activity (blood)	8 (recorded in only 14 cases)
Hepatomegaly	7
Limp and failure to stand	6
Sparse, coarse hair	5
Fissuring of lips	4
Constipation	3
Failure to gain weight	3

GRAPH 1

Comparison of Vitamin A Tolerance* in Case 1 with that of Normal Child†



* Vitamin A tolerance test was performed by administering orally 6,000 u. vitamin A/lb. body wt. (contained in 0.1/cc. Oleum Percomorphum) after drawing a control blood. Blood specimens are then taken 3, 6, 9 and 12 hr. after the ingestion of the vitamin.

† Mean value taken from the studies of Sobel, Besman and Kramer.[14]

A vitamin A tolerance test was performed after the administration of 0.1 cc. of oleum percomorphum/lb. body weight (2.5 cc. total). The results are shown graphically (graph 1).

A calcium-phosphorus balance study was performed.* The child was given a low calcium-phosphorus diet for 6 days before the 48 hr. collecting period. The results are shown on table 3.

Roentgenographic studies showed a normal skull, chest and pelvis. Intravenous pyelograms demonstrated a normal urinary tract, without evidence of calcification in the kidneys. RGs of the long

TABLE 3

CALCIUM AND PHOSPHORUS BALANCE STUDY; RESULTS INDICATE NEGATIVE CALCIUM BALANCE

	Ca (mg.)	P (mg.)
Intake	122.1	854
Output		
Urine	126.8	421
Stool	86.1	121.8
Balance	−90.8	+312.2

bones demonstrated thinning of the bony structures of both the forearms and the lower extremities with slight cortical thickening along the midportion of the shaft of the left ulna and of the lateral aspect of the right tibia. The epiphyseal lines showed an increase in density. (See Figs. 1 and 2.)

While in the hospital the child received no supplementary vitamins. Within 3 days his extremities were less painful and he no longer objected to being handled. He began to stand and walk around his crib. The perioral lesions disappeared, his general appearance improved and he was discharged after 9 days.

FIG. 1. Case 1. External cortical thickening along shaft of left ulna.
FIG. 2. Case 1. External cortical thickening along lateral aspect of right tibia.

* After 6 days of a measured calcium and phosphorus intake, the child was placed on a metabolic frame for 48 hr. Intake was accurately measured by means of duplicate food trays and the child was tubed for the collection of urine. Stools were accurately collected, the 48 hr. period being demarcated by means of orally ingested carmine red at the beginning and end of the 48 hr.

The patient was seen 5 mo. later. For the 1st 4 mo. of this period, the mother's apprehensiveness led her to withhold vitamin therapy. During the last month 10 drops of oleum percomorphum daily were given. Orange juice, however, had been taken for the entire 5 mo. A markedly changed infant was seen at this time. He was no longer irritable and was normally active and playful. The rash on his body along with the crusts on his lips had disappeared, as had the soft tissue swellings and painful extremities. He had gained 0.9 kg.

RGs of the extremities showed absence of cortical thickening of the right tibia while the periosteal change along the shaft of the left ulna was decreased in extent. The epiphyseal lines showed a diminution in density.

The total vitamin A level of the blood at this time was 60 μg % with 30 μg % in the alcoholic form.

In summary, the patient was admitted to the hospital because of irritability and failure to walk. He had been seen by his private physician and a radiographic examination of the extremities was made. Because of the detection of cortical thickening the child was referred to the hospital as a possible case of scurvy or leukemia. When on admission, lesions around the mouth resembling those of vitamin B complex deficiency were noted, a survey of the child's vitamin status in general was undertaken. It was then that the excessively high vitamin A plasma level was discovered.

Case 2: N.S., a 17 mo. old white girl, was admitted with the chief complaints of anorexia, irritability, refusal to walk and constipation. She had been hospitalized on 2 previous occasions.

She was first admitted at the age of 4 mo. because of a 6 wk. period of diarrhea and intermittent fever. There had been several changes of formula but the child had been receiving a comparatively constant normal vitamin intake. Studies in the hospital did not definitely prove that the child had celiac disease, but she was nevertheless discharged on a modified celiac regimen which included nutramigen®,* carrots and bananas, scraped apple, chicken, liver, lamb chop and pot cheese plus an increased vitamin intake.

At the age of 10 mo., she was readmitted because of slight regression in development and enlargement of the head. Diagnoses considered at this time were early rickets and beginning hydrocephalus. There was only inconclusive evidence for both diagnoses. Early roentgenologic changes and a slight elevation of the alkaline phosphatase (16.7 Bodansky u.) suggested rickets. Slightly dilated ventricles on pneumoencephalogram and ventriculogram suggested hydrocephalus. She was discharged to be observed further.

Nutritional history at this time revealed that since the time of discharge the child had been receiving in addition to the prescribed celiac diet, the following daily vitamin intake: 1 teaspoon each of oleum percomorphum and drisdol®,† 200 mg. of ascorbic acid and 30 drops of multi-beta®‡. Her total vitamin A intake was estimated to be approximately 240,000 u./day.

She did well for 2 additional months on the preceding dietary and vitamin intake, but then began to refuse all foods except orange juice, pineapple juice, apple sauce and water. She became quite irritable, slept poorly and did not walk well "because of weakness." Feces became small and hard. She was readmitted at the age of 17 mo., having lost 1.8 kg. in the 6 wk. prior to hospitalization.

At this time, she was thin, undernourished and irritable but in no acute distress. She sat up well but refused to stand alone. Positive physical findings were limited to the head; it was somewhat enlarged, with a prominent forehead, an asymmetrically placed anterior fontanelle, and a paucity of scalp hair.

It was during this admission that roentgen findings characteristic of hypervitaminosis A were seen. "The tibiae present evidence of a definite cortical thickening essentially subperiosteal in nature; subperiosteal thickening of the ulnae is also present and more pronounced on the right." (See Figs. 3 and 4.)

Additional studies of the blood revealed normal values for calcium and phosphorus (12.4 mg. %

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* Nutramigen (Mead Johnson) is a food containing predigested protein (a pancreatic casein hydrolysate, Amigen) combined with balanced amounts of carbohydrate, fat and minerals.

† Drisdol in propylene glycol (Winthrop-Stearns) is a stable, clear solution of pure crystalline vitamin D_3. It contains 10,000 U.S.P. u. of vitamin D/gm. or 250 u./drop, but no vitamin A.

‡ Multi-Beta (White Laboratories) is a liquid vitamin B complex concentrate. Each cc. contains 2.5 mg. thiamine chloride, 0.5 mg. riboflavin, plus other members of the B complex.

and 4.6 mg. %), and elevated serum alkaline phosphatase (16.3), normal vitamin C level (1.22 mg. %), high cholesterol (265 mg. %).

The child remained a feeding problem, refusing to eat and vomiting intermittently. Since 2 urine cultures yielded Esch. coli, she was given a course of sulfathiazole following which the urine cleared. The hydrocephalus did not increase.

The osseous changes in the roentgen films were variously interpreted. Some of the explanations offered included scurvy, chronic osteomyelitis, hyperparathyroidism and hypervitaminosis D. Because of the last possibility the child was sent home on a minimal vitamin intake to be observed for further changes.

For the next 4 mo. she did very well on a normal diet after a reduced vitamin intake. Her appetite improved markedly and she gained 2.7 kg. She did, however, have frequent colds and because of this was readmitted at the age of 21 mo. for a tonsillectomy. Physical examination at this time revealed a normal girl; the surgical procedure was performed uneventfully.

FIG. 3. Case 2. External cortical thickening of both tibiae and right fibula.

FIG. 4. Case 2. External cortical thickening of both ulnae.

The child did very well thereafter, her various symptoms gradually disappearing, and RGs of her upper extremities taken at the age of 4½ yr. showed no abnormalities.

In summary, therefore, evidence in Case 2, almost certainly indicating the presence of hypervitaminosis A, consists of the history of excess vitamin A intake, the characteristic clinical and roentgenographic findings and the disappearance of symptoms after cessation of high vitamin A intake. The diagnosis was not made or even suspected while the child was under observation, but was made in retrospect owing to the experience in Case 1.

DISCUSSION

Several interesting facts are brought out by the biochemical studies of the first case. The fasting level of total plasma vitamin A was 835 μg. %. This is the highest fasting vitamin A level reported in the literature. A second fasting vitamin A level was found to be 675 μg. %. Of this latter value, it was determined by partition studies that 454 μg. or 67.3% was in the form of the alcohol and only 221 μg. or 32.7% was present as the ester. This result may be contrasted with that obtained in clinical studies in the laboratory when high levels of vitamin in the blood were produced in normal

infants after administration of an aqueous concentrate of vitamin A. In such children, the main portion of the rise was found in the ester fraction, while the alcohol level constituted but 20% of the total (results to be published in subsequent reports).

This is in agreement with the work of Popper and his coworkers[15] who showed that in normal controls only 20% of the total vitamin A of the blood was in the ester form and that after administration of large amounts of vitamin A concentrate the rise in total vitamin A was due mainly to a rise in the ester portion.

Popper also showed that whereas the total vitamin A dropped only slightly in patients kept for several days on a vitamin A-deficient diet, the alcohol level dropped significantly producing a relative increase in the per cent of esters.

With these facts in mind, several speculations can be made. It has been suggested that vitamin A is transported from the intestine to the liver in an esterified form and stored there in this manner. There an hepatic esterase is present which converts the vitamin A ester to an alcohol after which it is released to the blood in the latter form. The blood vitamin A alcohol therefore represents vitamin A released from the liver and is a reflection of liver storage of the vitamin.[15] The fact that the bulk of the rise of vitamin A in the first case was due to the alcoholic portion plus the fact that in depletion experiments the main fall in vitamin A occurs in the alcohol fraction tends to substantiate this. The ester portion appears to rise only in response to an acute increase in vitamin A intake, e.g., after artificial administration of large amounts of vitamin A concentrate. It appears therefore that Popper is correct in stating that the vitamin A alcohol level is a better index of hypervitaminosis A than the total vitamin A level.

The vitamin A tolerance test, which was performed on the first patient, demonstrated that despite an initial high level of vitamin A, there occurred a marked rise in the plasma level. This increase was more than one usually finds in normal children. There was only a slight drop in the level after 12 hours. The liver in this child appeared to be normal as measured by a number of liver function tests. This indicated that the body stores must have been saturated with vitamin A and therefore deposition of vitamin A could have proceeded only at a slower rate.

Davis and Moore,[16] conducting experiments with rats, gave one group of animals large but nontoxic doses of vitamin A concentrate and noted high stores of vitamin A in the liver. To another group of animals they gave toxic amounts of vitamin A concentrate and their results showed essentially the same stores of vitamin A in the livers of these animals despite the fact that they developed signs and symptoms of vitamin A intoxication. It was their opinion that the syndrome in rats does not depend on the absolute amount of vitamin A present in the body but rather on the ingestion of the vitamin at a greater rate than that which could be stored by the liver or eliminated by the organism.

Sobel et al.[17] in 1948 gave evidence that the transfer of vitamin A to tissues was a function of the concentration in the plasma. This was shown by the following means: higher values of vitamin A were obtained both in the blood and the milk of lactating mothers when they were given aqueous rather than oily vitamin A preparations. Furthermore, if the blood level of the vitamin was raised to higher levels by increasing the dosage of the oily preparation, the amount of vitamin A in mother's milk was increased to corresponding levels.

On the basis of the preceding biochemical evidence suggesting saturation of storage

depots in hypervitaminosis A and the controlled clinical evidence that high plasma levels of vitamin A will pass various tissue barriers in the body, it is suggested that high permanent plasma levels may alter the metabolism of certain tissues, in particular that of bone. Here vitamin A is needed in moderate quantities but when present in overabundance, pathologic changes involving the epiphyseal and appositional bone growth occur. These consist of increased density of the epiphyseal lines and cortical thickening. The latter apparently is the cause for the tenderness of the extremities which is seen clinically.

Wolbach,[18] in a classic article in 1947, discussed the histologic findings in hypervitaminosis A as found in rats and guinea pigs. His investigations indicated that there was a speeding up of the metabolism of epiphyseal cartilage cells, resulting in their rapid maturation, degeneration and death. There was an increase in epiphyseal bone formation and at the same time, the shafts of the bones were being remodelled with bone from the epiphyses and from apposition bone growth. The resorption of bone, however, was greater than its formation and therefore there was an apparent lag in calcification. Fractures then occurred because the newly deposited bone did not have the requisite firmness to meet the varied stresses ordinarily withstood by normal bones. Wolbach states that he found no cause for these histologic changes in the parathyroids, thyroids, adrenals or pituitaries of his animals, and he concluded from his tissue studies that they probably were due to a local effect of the vitamin.

At the present time, there is no absolute evidence that the osseous findings in humans are identical with those described above by Wolbach. No biopsy or other pathologic material has been studied and the RGs do not show absolute signs of accelerated growth or excessive resorption of bone. On the basis of the calcium balance on the first patient which was instituted six days after he was placed on a low calcium-phosphorus diet and which showed a negative calcium balance, it can only be hypothesized that bone resorption in humans with hypervitaminosis A takes place more rapidly than deposition. It is realized, however, that this balance study was performed during only one particular stage of the disease. Further studies are necessary to determine whether a negative calcium balance is characteristic of all stages of hypervitaminosis A. One might speculate that if patients with hypervitaminosis A were to go undetected and the high doses of vitamin A were to be continued for a sufficient length of time, the changes found in animal experiments might occur.

Differential Diagnosis

The diagnosis of hypervitaminosis A depends upon the following points:

A. The age of onset is usually after the first year of life. (There are two possible reasons for this: absorption of oily preparation of vitamin A is poorer in young infants;[14] and possibly a long latent period is necessary for onset of toxic symptoms.)

B. The most common presenting symptoms are: irritability, anorexia, loss of hair, pruritis, tender extremities producing disturbances in gait and painful soft tissue swellings.

C. RGs reveal cortical thickening involving the long bones, particularly the ulnae.

D. The diagnosis is confirmed by the eliciting of an excessive vitamin A intake and the finding of a high plasma vitamin A level.

E. Symptoms disappear rapidly when vitamin A administration is discontinued.

Hypervitaminosis A may be commonly confused with several disorders. This is emphasized by the fact that in the two cases reported here as well as in the case reports reviewed, several other diagnostic possibilities were first considered.

The relatively new syndrome, infantile cortical hyperostosis, was first described by Caffey and Silverman[19] and then by Smyth et al.[20] The two conditions resemble one another and there are many who believe, because of the similarity of roentgen findings, that they are but variations of the same pathologic process. Although it is much too early to create rigid differential criteria, it is possible to present preliminary distinguishing points which are present in infantile cortical hyperostosis. These include absence of a history of excess vitamin A intake; age of onset before six months; fever usually present accompanied by high sedimentation rate and leukocytosis; the mandible is always involved; pleural effusions occur in many cases; plasma vitamin A level is normal, and symptoms do not disappear when vitamin A is discontinued.

The periostitis found in congenital syphilis resembles the roentgenologic picture of hypervitaminosis A. However, the initial difficulty in differentiation is resolved by routine clinical and serologic studies.

The nonspecific symptoms of anorexia, irritability, weight loss, painful extremities and disturbances in gait accompanied at times by subperiosteal elevations may suggest leukemia. The differential points with respect to the radiographic changes include the findings in leukemia of transverse bands of diminished density in the metaphyses of long bones, osteolysis and osteosclerosis, all of which are lacking in hypervitaminosis A.[21, 22]

Although immediate aid in the differentiation of scurvy and rickets from hypervitaminosis A may be obtained from the history of a deficient vitamin intake in contrast to an excessive one, certain aspects of the clinical and roentgenologic pictures may be confusing.

In scurvy, one of the most characteristic symptoms is marked tenderness of extremities. This, together with subperiosteal calcification seen during the healing stages may cause confusion. The following points may be helpful: presence of swelling, redness and sponginess of gums; tendency towards hemorrhage; and characteristic roentgenographic changes in the ossification centers and metaphyses during the active stages of the disease.

Healing rickets occasionally present subperiosteal bone proliferation. However, the characteristic roentgenographic changes in this disease are, of course, located at the epiphyseal plate.

Marked restlessness and irritability along with painful extremities and pruritis may point to the possibility of acrodynia. Certain features of acrodynia serve to differentiate the two conditions: pink coloration of hands and feet; profuse perspiration; hypotonia; hypertension; loss of teeth and nails; absence of roentgenographic bone changes; and presence of abnormal amounts of mercury in the urine.[23]

Hypervitaminosis D should not be overlooked in the differential diagnosis since patients who are taking excess vitamin A are usually ingesting proportionate increases in vitamin D. The literature concerning the quantities of vitamin D necessary for intoxication of infants and children is scanty. Conducting experiments with dogs and human adults, Steck and his coworkers[24] concluded that in both the minimum toxic dose was 20,000 I.U./kg./day. Hess et al.[25] administered 21 to 52 times the prophylactic dose for periods of 6 to 8 months and observed no deleterious effects. Wolfe[26] gave large doses of the vitamin to an infant with spina bifida and meningocele in order to determine

his tolerance. It was his opinion that 85,000 U.S.P. u./kg./day given for 12 consecutive days was probably the toxic dose. He concluded that "there is a wide margin of safety in the use of large daily doses or single massive doses of vitamin D in infants and children."

The clinical and laboratory picture differs from that of poisoning with vitamin A. Debré,[27] summarizing his findings in 21 cases of hypervitaminosis D in children, points out that there is usually a sudden appearance of severe anorexia, nausea, vomiting, thirst and constipation. The children become progressively dehydrated, irritable and depressed, and gradually sink into a stupor. The laboratory data reveals a constant high blood pressure, an almost always greatly elevated calcium and phosphorus and signs of renal damage: albumin and formed elements in the urine, a high urea nitrogen, and abnormal kidney function tests. This clinical picture in children is confirmed by Thatcher[28, 29] with his two case reports and by Ross and Williams[30] who reported four cases in infancy.

The pathology which is responsible for this syndrome consists of widespread metastatic calcification involving the kidney tubules, heart and blood vessels, gastric mucosa, lungs and pancreas.[31]

Although the ingestion of vitamin D cannot be definitely ruled out as contributing partly to the clinical picture in both of these reported cases, it is the authors' opinion that the vitamin, if anything, played a minor role. The dosages given—in the first case only 20,000 u./day and in the second only 75,000 u./day—were both much lower/kg. body weight than those quoted; the clinical pictures were almost totally different, and there were no signs of metastatic calcification, high blood pressure, alteration of calcium-phosphorus levels, or renal dysfunction. Toomey and Morissette,[9] in a clinical experiment on their case of hypervitaminosis A, ruled out the factor of excess vitamin D completely.

Summary

Two cases of hypervitaminosis A have been presented together with a review of experimental and clinical literature.

The first case presented the highest reported fasting plasma vitamin A level, the increase being chiefly due to a high vitamin A alcohol fraction. This elevated level of alcoholic vitamin A probably denotes large stores of vitamin A in the liver and data have been given to show that it is a better index of hypervitaminosis A than is the total vitamin A level. In addition, evidence has been presented that the toxic factor in hypervitaminosis A is the permanent elevated plasma vitamin A level.

The similarity between the experimental studies in animals and the observations in the authors' first case has been shown.

The important points necessary for making a diagnosis of hypervitaminosis A have been discussed and several similar conditions have been differentiated.

It cannot be emphasized too strongly that excess vitamin intake may be as dangerous as a deficient intake.

Acknowledgment

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Addendum

Since this manuscript was submitted for publication, one additional case of vitamin A poisoning has been decribed (Wyatt, T. C., Carabello, C. A., and Fletcher, M. E., Hypervitaminosis A, J.A.M.A. **144**:304, 1950). With the addition of this case which has typical clinical, chemical and roentgenologic findings, a total of 17 cases representing this syndrome have now been recorded.

References

1. von Drigalski, W., Über Schadigungen durch Vitamin A, Klin. Wchnschr. **12**:308, 1933.
2. Collazo, J. A., and Sanchez Rodriguez, J., Hypervitaminose A, Klin. Wchnschr. **12**:1732 and 1768, 1933.
3. Finucci, V., Pathologic regeneration and inflammatory reaction in hypervitaminosis A, Arch. ital. chir. **41**:480, 1935.
4. Vedder, E. B., and Rosenberg, C., Concerning toxicity of vitamin A, J. Nutrition **16**:57, 1938.
5. Chalier, J., and Jeune, M., L'hypervitaminose A experimentelle du cobaye, Compt. rend. Soc. de Biol. **129**:604, 1938.
6. Russo, F., Experimental and clinical studies of hypervitaminosis A, Fisiol. e Med. **10**:265, 1939.
7. Clausen, S. W., Pharmacology and therapeutics of vitamin A, J.A.M.A. **111**:144, 1939.
8. Josephs, H. W., Hypervitaminosis A and carotinemia, Am. J. Dis. Child. **67**:33, 1944.
9. Toomey, J. A., and Morissette, R. A., Hypervitaminosis A, Am. J. Dis. Child. **73**:473, 1947.
10. Rothman, P. E., and Leon, E. E., Hypervitaminosis A, Radiology **51**:368, 1948.
11. Dickey, L. B., and Bradley, E. J., Hypervitaminosis A, Stanford M. J. **6**:345, 1950.
12. Fried, C. T., and Grand, M. J. H., Hypervitaminosis A, Am. J. Dis. Child. **79**:475, 1950.
13. Caffey, J., Chronic poisoning due to excess of vitamin A, Pediatrics **5**:672, 1950.
14. Sobel, A. E., Besman, L., and Kramer, B., Vitamin A absorption in newborn, Am. J. Dis. Child. **77**:576, 1949.
15. Popper, H., Steigmann, F., Dubin, A., Dyniewicz, H. A., and Hesser, F. P., Significance of vitamin A alcohol and ester partitioning under normal and pathologic circumstances, Proc. Soc. Exper. Biol. & Med. **68**:676, 1948.
16. Davis, A. W., and Moore, T., Vitamin A and carotene: Distribution of vitamin A in organs of normal and hypervitaminotic rats, Biochem. J. **24**:288, 1934.
17. Sobel, A. E., and others, Aqueous dispersions of fat soluble vitamins, Federation Proc. **8**:259, 1949.
18. Wolbach, S. B., Vitamin A deficiency and excess in relation to skeletal growth, J. Bone & Joint Surg. **29**:171, 1947.
19. Caffey, J., and Silverman, W., Infantile cortical hyperostoses, Am. J. Roentgenol. **54**:1, 1945.
20. Smyth, F. S., Potter, A., and Silverman, W., Periosteal reaction, fever and irritability in young infants: New syndrome? Am. J. Dis. Child. **71**:333, 1946.
21. Silverman, F. N., Skeletal lesions in leukemia, Am. J. Roentgenol. **59**:819, 1948.
22. Dale, J. H., Leukemia in childhood, J. Pediat. **34**:421, 1949.
23. Warkany, J., and Hubbard, D. M., Mercury in urine of children with acrodynia, Lancet **1**:829, 1948.
24. Steck, I. E., Deutsch, H., Reed, C. I., and Struck, H. C., Further studies on intoxication with vitamin D, Ann. Int. Med. **10**:951, 1937.
25. Hess, J. H., Poncher, H. G., Dale, M. L., and Klein, R. I., Viosterol in prophylactic and therapeutic dosage, J.A.M.A. **95**:316, 1930.
26. Wolfe, I. J., Safety of large doses of vitamin D in prevention and treatment of rickets in infancy, J. Pediat. **22**:707, 1943.
27. Debré, R., Toxic effects of overdosage of vitamin D_2 in children, Am. J. Dis. Child. **75**:787, 1948.
28. Thatcher, L., Hypervitaminosis D with report of fatal case, Edinburgh M. J. **38**:457, 1931.
29. Thatcher, L., Hypervitaminosis D, Lancet **1**:20, 1936.
30. Ross, S. G., and Williams, W. E., Vitamin D intoxication in infancy, Am. J. Dis. Child. **58**:1142, 1939.
31. Mulligan, R. M., Metastatic calcification associated with hypervitaminosis D and haliphagia, Am. J. Path. **22**:1293, 1946.

SPANISH ABSTRACT

Intoxicación de Vitamina "A"

Los autores reportan dos casos de intoxicación de vitamina A y conjuntamente revisan la data experimental y clinica publicada. El primer caso reportado presentó la mayor concentración de vitamina A del plasma, siendo este aumento principalmente debido a la fracción alcoholica de vitamina A. Esta elevación de la fracción alcoholica posiblemente indica la presencia de grandes reservas de vitamina A en el higado. Los autores presentan data demostrando que la fracción alcoholica es un indíce mas exacto de hiperavitaminosis, que la concentración de vitamina A total. Además, se presenta evidencia indicando que el factor toxico de la hiperavitaminosis es la elevación permanente del nivel de vitamina A del plasma.

Se señala la similaridad entre los estudios experimentales en animales y las observaciónes reportadas en el primer caso.

Los autores destacan los puntos importantes y necesarios para el diagnóstico de la hiperavitaminosis A, y sé discute el diagnóstico diferencial con otras condiciones similares.

En conclusión, sé indica que tanto un exceso de vitamina A es tan peligroso como la ingestión deficiente.

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VITAMIN E BLOOD LEVELS IN PREMATURE AND FULL TERM INFANTS

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VITAMIN E (tocopherol) plays an important metabolic role in the animal organism.[1] The deficiency state experimentally or accidentally induced in laboratory and farm animals is characterized by a variety of manifestations. These vary from encephalomalacia and exudative diathesis in the chick to fetal resorption, muscular dystrophy, testicular damage and other effects in mammals. As a rule, the metabolic dysfunctions and histopathologic lesions are most readily produced during early phases of the life span.

Whether a state of E-avitaminosis ever occurs in man still remains a matter of speculation. However, there exists an extensive but highly controversial literature concerning the efficacy of vitamin E in certain clinical states, such as coronary disease, fibrositis and menopausal symptoms.[2] These, for the most part, are related to dysfunctions of later life. Serum tocopherol levels in normal adults and in those suffering from disease states have been studied extensively by Harris et al.,[3] Darby et al.[4] and others. These studies indicate that the mean serum level of tocopherol is less than normal in a group of malnourished individuals and in patients with disease states associated with impaired absorption of fats—sprue, biliary obstruction and fibrocystic disease of the pancreas. Serum tocopherol levels are moderately high in hypertensive cardiovascular disease and unusually high in certain metabolic disorders characterized by hypercholesterolemia. However, little attention has been given to the tocopherol status during prenatal and early postnatal life in man, corresponding to that period when deficiency symptoms are most easily produced in the experimental animal. Using macrochemical methods, Straumfjord and Quaife[5] and Dju[6] have demonstrated that tocopherol levels of cord blood and fetal tissues, respectively, are much lower than those of adult human blood and tissues. In accord with these findings are the studies of Mason and Bryan[7] demonstrating that, in the rat, transfer of vitamin E across the placental barrier is decidedly limited, but that its passage across the mammary barrier occurs to a much greater extent.

Quaife, Scrimshaw and Lowry[8] have recently developed a micromethod for the chemical determination of serum tocopherols,* requiring minute quantities of blood. The studies reported here represent an application of this micromethod to a study of the blood-tocopherol status in premature and full term infants and their mothers.

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* The terms vitamin E and tocopherol are used synonymously. Since the method measures the total tocopherols, alpha, beta, gamma and delta, the term serum tocopherol, or serum tocopherols, is preferable.

Method and Materials

Method: The micromethod for assay of total tocopherols, as described by Quaife, Scrimshaw and Lowry,[8] was used. Briefly, the technic consists of "(1) precipitation of protein with ethyl alcohol and extraction of tocopherols into xylene: (2) dilution of an aliquot of xylene extract with αα′ dipyridyl in n-propyl alcohol: (3) measurement of light absorption due to carotenoids at 460 mμ; and (4) addition of ferric chloride to the Beckman cuvette and measurement of absorption at 520 mμ." Analyses were done in duplicate, and the results were averaged. The precision of the method is within 5% on duplicate samples.

Materials: The full term infants in this study were those admitted to the newborn nurseries of the Strong Memorial and Rochester Municipal Hospitals. All infants were above 2,250 gm. birth weight and all were in good physical condition. Samples were taken on the first or second day of life, prior to the first feeding, and again on the fourth and sixth days of life. For those infants not nursing, the formula given was the usual evaporated milk, water (1:2 ratio), and carbohydrate formula. In about two thirds of the cases, blood was drawn from the mother as well as from the infant to permit a comparison of tocopherol levels.

The older infants, up to the age of 8 mo., were studied at an outside clinic. As in the group of newborn infants, samples were taken on the mother at the same time.

The premature infants studied were those admitted to the premature nursery of the Strong Memorial and Rochester Municipal Hospitals. Their birth weights ranged from 780 to 2,250 gm. All these infants were receiving a formula of alacta®,* water and carbohydrate. All received supplementary ascorbic acid, 50 mg. daily, and oleum percomorphum, 10 drops daily. Several infants received navitol®, or drisdol®, and 1 infant received ferrous sulfate. Four premature infants died between the first and eighth day of life.

Samples were obtained by heel or finger puncture and the free-flowing blood was drawn into a piece of glass tubing, 2 mm. inside diameter and 10 to 15 cm. in length. After retraction of the clot, the samples were transferred to 13 x 100 mm. pyrex test tubes, centrifuged, and the supernatant serum aliquoted for analysis. These aliquoted samples may be stored up to 8 wk, at −20°C, without loss of tocopherol.

Results and Discussion

Table 1 and chart 1 present the data on the mothers of the newborn infants; this group is divided into (1) mothers who were nursing their infants and (2) mothers whose infants were receiving an artificial formula.

An accepted serum tocopherol level for the normal adult based on the studies of Harris et al.,[3] is 1.04 mg./100 cc. (S.D. ± 0.32). According to Straumfjord and Quaife[5] and Scrimshaw, Greer and Goodland,[9] there is a gradual increase in the tocopherol level of women during pregnancy rising to 1½ to 2 times the normal adult level by the end of the ninth month of gestation, or within the first two days following parturition. The tocopherol levels of 2.05 mg./100 cc. in the nonnursing mothers and of 1.82 mg./100 cc. in the nursing mothers, do not represent a significant difference ($P = 0.22$, table 1) but do illustrate the high serum levels at the time of parturition. This rise in serum tocopherol may reflect the physiologic demand of both the fetus and mother for increased tocopherol, or may reflect a release of tocopherol from the maternal storage depots in the liver and fatty tissue in an effort to increase the placental and mammary transfer of tocopherols to the fetus and infant, respectively.

During the first six days following parturition, the group of nursing mothers maintained slightly lower serum tocopherol levels when compared to the nonnursing group. This difference is statistically significant only on the fourth day ($P = 0.05$), when the mean tocopherol level of the nursing mothers fell to 1.63 mg./100 cc. as compared to

* Alacta® consists of skimmed milk powder 57% and whole milk powder 43%.

TABLE 1

MEAN MATERNAL SERUM TOCOPHEROL LEVELS

	Serum Tocopherol mg./100 cc. Serum ± S.D.				
	Days or mo. postpartum				
	2 days	4 days	6 days	1–4 mo.	5–8 mo.
Nursing Mothers	1.82±0.59 N=28	1.63±0.51 N=24	1.86±0.55 N=24	1.44±0.52 N=7	1.36±0.37 N=7
Nonnursing Mothers	2.05±0.68 N=23	1.93±0.48 N=24	1.92±0.50 N=20	1.18±0.26 N=15	1.28±0.16 N=8
	t=1.23 P=0.22	t=2.01 P=0.05	t=0.36	t=1.13 P=0.27	t=0.46

N = no. of observations.

P = probability of significant difference. A value of 0.05 or less is generally regarded as indicating a significant degree of difference.

$$t=\frac{\bar{X}_1-\bar{X}_2}{\frac{N_1+N_2}{N_1+N_2-2}\sqrt{\frac{\sigma_1}{N_1}+\frac{\sigma_2}{N_2}}}$$

$$\text{Standard Deviation (S.D.)}=\sqrt{\frac{\Sigma(x-\bar{x})^2}{N-1}}=\sigma$$

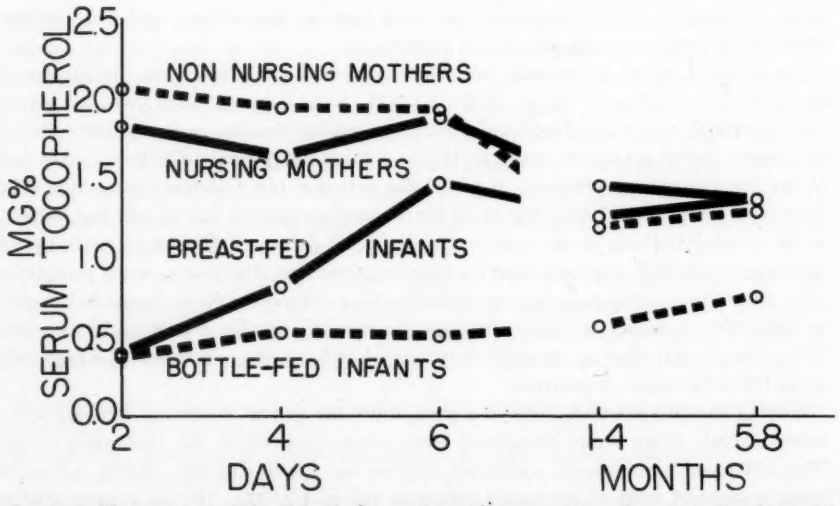

CHART 1. Mean serum tocopherol levels for nursing and nonnursing mothers as well as breast-fed and bottle-fed infants during first postpartum week, and at periods of 1-4 mo. and 5-8 mo. post partum.

TABLE 2

MEAN SERUM TOCOPHEROL LEVELS OF NEWBORN INFANTS DURING HOSPITAL STAY

Diet	Serum Tocopherol mg./100 cc. serum ± S.D.				
	Age				
	2 days	4 days	6 days	1–4 mo.	5–8 mo.
Breast-Fed	0.38±0.18 N=40	0.81±0.37 N=34	1.46±0.63 N=34	1.25±0.22 N=7	1.35±0.29 N=7
Bottle-Fed	0.37±0.15 N=37	0.52±0.22 N=34	0.50±0.23 N=37	0.53±0.23 N=20	0.75±0.14 N=10

the more stable level of 1.93 mg./100 cc. in the nonnursing group. This significant difference may reflect a large transfer of tocopherols, through the colostrum, from the mother to her nursing infant.

In striking contrast to the high maternal serum levels, the newborn infants on the first or second day, and before they had received any supplementary tocopherol through their feedings, had a mean level of 0.38 mg./100 cc. (table 2, chart 1); this is approximately one fifth that of the maternal value. As an explanation for this difference several possibilities might be offered: (1) the maternal placenta may permit only a limited transmission of tocopherol, (2) the fetus possesses a regulatory mechanism preventing its accumulation beyond limited amounts or (3) the rate of utilization of tocopherol by the fetus is relatively greater than that of the mother.

Subsequent to birth, the breast-fed infant has access to another and presumably more adequate source of tocopherol. The colostrum of human milk has been shown by Quaife[10] to be rich in tocopherols, containing as much as 3.6 mg. tocopherols/100 cc. colostrum (table 3). The rapidly rising level of the serum tocopherol in breast-fed infants, reaching a mean value of 1.46 mg./100 cc. by the sixth day of life, is ample evidence of the large quantities of tocopherol crossing the mammary barrier in the colostrum and early breast milk (table 2, chart 1).

TABLE 3

ESTIMATED TOCOPHEROL CONTENTS OF VARIOUS INFANT DIETS

Diets	Tocopherol mg./100 cc.
*Human Milk (1–8 days post partum)	0.4–3.6
*Human Milk (later periods)	0.15
†Cow's Colostrum	0.6
†Cow's Milk	0.12
‡Evaporated Milk Formula 1:2	0.10
Alacta Formula	0.04

* From data of Quaife[10]

† From graph by Hickman[2]

‡ From data of Harris et al.[11]

In direct contrast to the rising levels of the breast-fed infant are the relatively stationary levels of the artificially fed infant (table 2, chart 1) on a formula containing approximately 0.1 mg. tocopherols/100 cc. formula (table 3).

Chart 1 represents graphically the mean tocopherol levels in nursing and non-nursing mothers and their infants in the newborn period and, on the right hand side of the graph, data gathered on older infants up to 8 months of age. Although by this time

TABLE 4

MEAN SERUM TOCOPHEROL LEVELS OF PREMATURE INFANTS DURING HOSPITAL STAY

Days of age	No. of Patients	No. of Observations	Serum Tocopherol mg./100 cc. ± S.D.
1–10	21	30	0.43±0.19
11–20	15	22	0.28±0.15
21–30	9	14	0.17±0.15
31–40	5	9	0.09±0.09

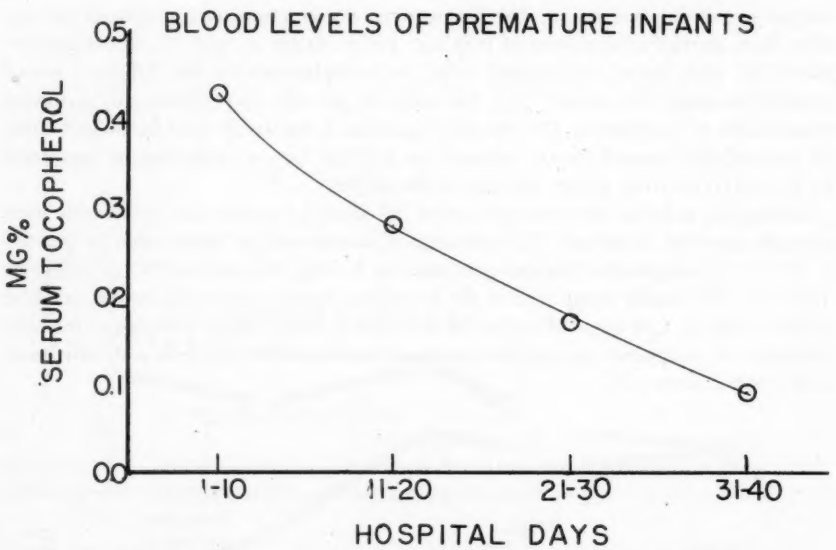

CHART 2. Mean level of serum tocopherols in premature infant during 1st 40 days of age.

the tocopherol content of breast milk is approximately 0.11 to 0.15 mg./100 cc.,[10] and approaches the tocopherol content of an evaporated milk formula (table 3), the breast-fed infants maintain much higher tocopherol levels than the artificially-fed infants (table 2, chart 1), whose serum levels, though slowly rising, are still below 1 mg./100 cc. At what age the serum tocopherol level of the artificially-fed infant will reach the normal adult value of 1.04 mg./100 cc. (± 0.32) has not been determined.

The maternal levels show a gradual fall during this later period (table 1, chart 1), the

nonnursing mothers being slightly, but not significantly, lower than the nursing mothers.

Table 4 and chart 2 present the results of the third phase of this study, designed to show the effect of an artificial skimmed milk formula on the serum tocopherol level of the premature infant.

The initial mean serum level of 0.43 mg./100 cc. in the premature infant corresponds closely to the mean of 0.38 mg./100 cc. (table 2) in the full term infant. Serum levels, however, may not reflect the true state of storage or distribution of tocopherol, and there is need for more specific information on the tocopherol content of the tissues in the fetus and full term infant.

Chart 2 shows the gradual fall in serum tocopherol which occurs in the premature infant on an artificial skimmed-milk formula. Each point on the curve represents the

TABLE 5

PROBABILITY VALUES FROM STUDENT'S t TEST FOR SIGNIFICANCE APPLIED TO TOCOPHEROL DATA FOR PREMATURE INFANTS

Days of age	1–10	11–20	21–30	31–40
1–10	—	t = 3.05 P = <0.01	not det'm	not det'm
11–20	t = 3.05 P = <0.01	—	t = 1.60 P = 0.12	t = 4.0 P = <0.01
21–30	not det'm	t = 1.60 P = 0.12	—	t = 1.43 P = 0.19
31–40	not det'm	t = 4.0 P = <0.01	t = 1.43 P = 0.18	—

mean of the serum levels of not less than five premature infants, or nine separate observations.

It is readily noted that there is a steady decline in the mean tocopherol values reaching a level of 0.09 mg./100 cc. by the 31st to 40th day of life. The application of students' t-test, summarized in table 5, indicates that there is a significant difference in the serum level of tocopherol for all periods except the period of 11 to 20 days of age compared with the 21 to 30 days of age, where $t = 1.60$ and $P = 0.12$, and the period of 21 to 30 days of age compared with 31 to 40 days of age, where $t = 1.43$ and $P = 0.19$. This fall in the serum levels may represent the effect on the premature infant of three unrelated factors: (1) an inadequate supply of tocopherol, represented by the artificial formula containing approximately 0.04 mg./100 cc. tocopherol (table 3); (2) an excessive demand for tocopherol represented by the tremendous increase in body mass of the premature infant during the last trimester of intrauterine life and first several months of extrauterine life, during which time there may be an increased demand on his already low stores of tocopherol; and (3) a probable redistribution of tocopherol due to an increase of blood volume, and hemodilution.

The premature infant fed a formula low in tocopherol, and subjected to the increased demands of his own tissues, rapidly develops a low-serum tocopherol level which may

approach that which in the young experimental animal produces typical deficiency symptoms. Whether the maintenance of a critically low level of serum tocopherol for a considerable period of time preceding the institution of a mixed diet can exert a harmful effect, or influence the subsequent health of the young infant, remains to be ascertained. Although no dysfunction of infancy has been related to a deficiency of vitamin E, Owens and Owens[12] have presented suggestive evidence that retrolental fibroplasia may be arrested by tocopherol therapy, and György[13] has raised the question of the role of vitamin E in the pathogenesis of erythroblastosis fetalis. These are but indications of the need for more exhaustive exploration of the role of tocopherol in the nutritional program of the premature and full term infant.

Summary

Newborn infants showed serum tocopherol levels approximately one-fifth those of the maternal levels.

During the first six days after birth, the serum tocopherols of breast-fed infants increased much more rapidly than those of bottle-fed infants. These differences were still evident at 1 to 4, and at 5 to 8, months of age.

Premature infants fed an artificial formula low in vitamin E showed a rapid decline in serum tocopherol levels.

These studies confirm and amplify other evidence that placental transfer of vitamin E is decidedly limited while mammary transfer is much more extensive.

Acknowledgments

The authors wish to acknowledge the encouragement and helpful criticism of Dr. S. W. Clausen during the course of these studies, and the technical assistance of Miss Marian McMillan and Mrs. Robert Scholes.

References

1. Mason, K. E., Physiological action of vitamin E and its homologues, in Vitamins and Hormones, edited by R. S. Harris and K. V. Thimann, New York, Academic Press, Inc., 1944, vol. 2, p. 107.
2. Hickman, K. C. D., Vitamin E in medicine, Record of Chemical Progress **9**:104, 1948.
3. Harris, P. L., Hickman, K. C. D., Jensen, J. L., and Spies, T. D., Survey of blood plasma levels of vitamin A, carotene, ascorbic acid and tocopherols of persons in area of endemic malnutrition, Am. J. Pub. Health **36**:155, 1946.
4. Darby, W. J., and others, Plasma tocopherols in health and disease, Ann. New York Acad. Sc. **52**:328, 1949.
5. Straumfjord, J. V., and Quaife, Mary L., Vitamin E levels in maternal and fetal blood plasma, Proc. Soc. Exper. Biol. & Med. **61**:369, 1946.
6. Dju, Mei Yu, Unpublished data.
7. Mason, K. E., and Bryan, W. L., Placental and mammary transfer of vitamin E in rat, J. Nutrition **20**:501, 1940.
8. Quaife, Mary L., Scrimshaw, N. S., and Lowry, O. H., Micromethod for assay of total tocopherols in blood serum, J. Biol. Chem. **180**:1229, 1949.
9. Scrimshaw, N. S., Greer, R. B., and Goodland, R. L., Serum vitamin E levels in complications of pregnancy, Ann. New York Acad. Sc. **52**:312, 1949.
10. Quaife, Mary L., Tocopherols (vitamin E) in milk: Their chemical determination and occurrence in human milk, J. Biol. Chem. **169**:513, 1947.
11. Harris, P. L., Quaife, Mary L., and Swanson, W. J., Vitamin E content of foods, J. Nutrition **40**:367, 1950.

12. Owens, W. C., and Owens, E. U., Retrolental fibroplasia in premature infants. II. Studies on prophylaxis of disease: Use of alpha tocopherol acetate, Am. J. Ophth. **32**:1631, 1949.
13. György, P., and Rose, C. S., Tocopherol and hemolysis *in vivo* and *in vitro*, Ann. New York Acad. Sc. **52**:231, 1949.

SPANISH ABSTRACT

Niveles Sanguineos de Vitamina E en Prematuros y Niños a Termino

Los niveles de tocoferol del suero de niños recién nacidos fué aproximadamente la quinta parte de los niveles maternos.

Durante los seís primeros días siguientes al nacimiento, el tocoferol sanguineo de niños alimentados al pecho aumentó mas rapidamente que en los niños alimentados artificialmente. Estas diferencias aún eran evidentes a los 4 y 8 meses de edad.

Prematuros alimentados artificialmente con una formula baja en vitamina E demostraron una caída rapida de los niveles de tocoferol del suero.

Estos estudios confirman y amplifican evidencia demostrando que le pasaje placental de vitamina E es decididamente limitado, mientras que el pasaje mamario es mucho mas extensivo.

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PULMONOCARDIAC FAILURE

Report of a Case

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PULMONOCARDIAC failure is a distinct clinical entity in which patients with severe thoracic and/or spinal deformities eventually succumb to cardiac failure brought about by prolonged respiratory insufficiency. This syndrome has long been recognized in the foreign literature and has been called scoliotic or kyphoscoliotic heart disease.[1-6] However, few cases have been reported in this country,[7-9] the most comprehensive report being that of Chapman et al., in which the term "pulmonocardiac failure" is introduced.[7] The following case has many of the typical features of this syndrome as well as some unusual ones which will be discussed.

REPORT OF A CASE

Present Illness: G.H.C., a 10 yr. old white male, was admitted to Duke Hospital because of "shortness of breath" of 5 wk.' duration. His first admission was at the age of 12 wk. because of "sinking in of the chest" which had been noted 1 wk. previously. The child appeared normal at birth and weighed 3.0 kg. Delivery had followed a normal gestation in a healthy mother who was 25 yr. old. At the age of 11 wk. the mother noted that the thoracic cage "caved in" in the region of the lower end of the sternum with each inspiration. There was no cyanosis. Examination showed a bilateral deformity of the chest with fusion and unequal spacing of the ribs. There was a concavity measuring 3 × 3 cm. in the xyphoid region which was accentuated on inspiration. The remainder of the examination was negative except for a rapid heart rate. Roentgenograms of the spine showed a diffuse irregular spina bifida of practically every vertebra with numerous hemivertebrae. There was narrowing of the thoracic vertebrae and of the intercostal spaces.

The child was not seen again until his last admission at the age of 10 yr. His motor development during the interval was normal. However, his stature was always small. He had persistent shortness of breath and occasional periods of cyanosis of the lips associated with vomiting; these episodes became more frequent in the 3 yr. preceding his last admission. He had always had a rapid heart, precordial impulse being visible to the parents.

At the age of 8 yr., he developed pneumonia from which he slowly recovered under penicillin therapy despite an urticarial reaction. Also, during this acute episode, he was given digitalis for several days presumably because of a marked tachycardia. After this illness he developed respiratory infections more easily, and with these infections, attacks of asthmatic-like wheezing occurred.

Five weeks before his last admission, the boy had symptoms of a respiratory infection with mild cough for which he was given 3 daily injections of penicillin. He again developed an urticaria. He was then given aureomycin 50 mg. every 4 hr. but began to vomit the medication. Three weeks before admission the cough became worse, especially at night, occurring in severe paroxysms during which he could get relief only by assuming a position on his hands and knees. Two weeks before admission he was again given aureomycin with some improvement of the cough. However, he soon developed cyanosis and orthopnea severe enough to necessitate hospital admission. He vomited frequently during the 4 days prior to admission.

Past History: At the age of 4 yr. he was diagnosed as having abortive poliomyelitis with stiff neck and transient weakness of 1 leg. At 6 yr. he had a tonsillectomy and apparently tolerated the anesthesia (type unknown) well.

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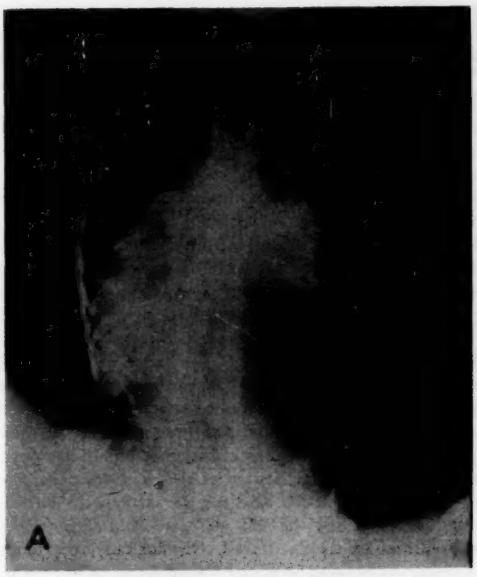
The family history was negative for congenital deformities and was otherwise noncontributory.

Physical Examination: Temperature 37°C. Blood pressure 100/60 mm.Hg. Wt. 26.8 kg. The patient was a small, thin, poorly developed male whose breathing was rapid and shallow. The skin was sallow with definite cyanosis. He was in obvious respiratory distress and was unable to lie flat. There was a congenital deformity of the ribs with a decrease in the PA diameter of the chest. The ribs were fixed and the vertical diameter of the thorax was shortened. The intercostal spaces were



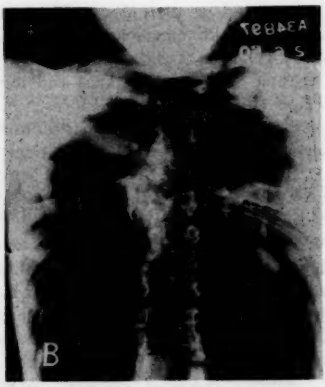


FIG. 1A. Chest RG showing abnormal diaphragmatic shadow obscuring heart outline and most of lungs. B. and C. RG of thoracic and lumbar spine with heart and lungs removed showing marked abnormalities of vertebral bodies with hemivertebrae, and abnormal origin of ribs.

narrow and chest movement with respiration was negligible. The neck was short and flexion was limited by the deformity, as was flexion of the entire spine. The percussion note was dull anteriorly, but resonant posteriorly and laterally. Occasional fine inspiratory rales were heard at the left base. The heart borders could not be determined by percussion. The rate was 140, the sounds were of fair quality without murmurs. There was an extremely loud and snapping pulmonary second sound. The liver was palpable 2 cm. below the costal margin and slightly tender. The nail beds were

cyanotic but clubbing was absent. There was slight pitting edema of the ankles. The right testis was undescended. The remainder of the examination was negative.

Accessory Clinical Findings: RBC 4.5 million/cmm. Hgb. 14 gm./100 cc. WBC 11.4 thousand/cmm. with 70 polymorphonuclear leucocytes, 20 lymphocytes and 10 monocytes. Urinalysis revealed a 1+ albumin, a trace of acetone and a few hyaline casts. Chest RGs showed deformities of the spine and thorax with the diaphragms situated high and almost completely obscuring the lungs in the frontal view. The heart shadow was also obscured by the diaphragms. No definite pulmonary lesion could be seen (Fig. 1A). Postmortem RGs of the entire spine showed marked congenital anomalies with numerous hemivertebrae. The fifth through the ninth ribs articulated with about 3 vertebrae on 1 side and with 4 vertebrae on the other. The lower thoracic and all lumbar vertebrae showed spina bifida and it was not possible to distinguish the separate vertebral bodies (Figs. 1B and 1C).

Electrocardiogram revealed a sinus tachycardia with a rate of 142. The record was interpreted as showing findings consistent with right axis deviation and right ventricular strain.

Hospital Course: The original impression was that the patient had cor pulmonale secondary to probable pulmonary fibrosis, and severe myocardial failure. He was placed in an oxygen tent and sedated with phenobarbital, with some improvement in color. Digitalization was started with digitoxin, the initial dose being 0.4 mg., the second dose 0.2 mg. and subsequent doses of 0.1 mg. were to be given 6 hr. apart until full digitalization was reached. His condition did not improve under this regime and on the day following admission penicillin therapy was begun because it was felt that he had pneumonia. In view of his previous history of urticaria from penicillin, pyribenzamine was also given. His condition steadily became worse, the orthopnea and cyanosis increased, the respirations became weaker and death occurred 50 hr. after admission.

Autopsy Findings: Pertinent autopsy findings were intrathoracic. On opening the chest, the heart was found pushed toward the anterior chest wall due to a malformed vertebral column and a high attachment of the diaphragm. There were 12 ribs on each side. The heart weighed 190 gm. and was normally formed, as were the great vessels. There was some dilatation of all chambers, but the most remarkable finding was marked hypertrophy and dilatation of the right ventricle. The right ventricular wall was thickened and measured 1 cm. near the base. All the valves were normal.

The lungs were small, the right weighing 200 gm. and the left 180 gm. Both upper lobes showed excrescences conforming to the irregularities of the chest wall. Histologically, the lungs showed acute congestion and edema. Foci of bronchopneumonia with early organization were present. It should be emphasized that neither interstitial pulmonary fibrosis nor arteriosclerosis were noted.

The liver and spleen showed passive congestion.

The left kidney was of normal size and weighed 100 gm. The right kidney was hypoplastic and weighed only 30 gm. An incidental finding was the presence of basophilic-staining material in the tubules which appeared like degenerated casts or epithelium.

The major abnormality was in the vertebral column. The usual number of vertebrae and ribs were present. However, there were hemivertibrae of the entire thoracic and lumbar spine. The vertebral bodies were irregular and alternated from left to right of the midline. Upon longitudinal sectioning, it was seen that the spinal cord was in its normal central canal. There were 2 lateral columns of ossification centers, separated in the midline by fibro-cartilage. All the bodies were assembled in a "brick laying" fashion.

Anomalous bony processes arose from vertebral bodies T3 and T4 and extended into the thoracic cage for about 5 cm. from both sides of the bodies. The left processes connected the anterior aspect of the vertebral bodies to the inner aspect of the third and fourth ribs. This segment of vertebral column was of such dimension that it occupied about half the anterior-posterior diameter of the chest.

The diaphragm was attached high on either side to the anomalous bony processes of T3 and T4. Two muscular and tendinous flaps ran down in oblique manner along the lateral borders of the sternum. These 2 flaps then met the sternal attachment of the diaphragm from the back of the xyphoid process, the costal portion from the inner aspects of the lower sixth rib on either side, and the lumbar portion from aponeurotic arches.

Final Anatomic Diagnoses: Double ossification centers in vertebral bodies; anomalous bony processes of third and fourth thoracic vertebral bodies; high and abnormal insertion of the diaphragm to the anomalous bones; right ventricular hypertrophy and dilatation; acute pulmonary congestion and edema, bilateral; passive congestion of spleen and liver; early organizing pneumonia;

focal tubular degeneration and hemosiderin deposition in the kidney, bilateral; hypoplasia of right kidney; cryptorchidism, right.

Discussion

Chapman, Dill and Graybiel in 1939 presented clinical and laboratory data in 12 patients, four ending fatally, who suffered from pulmonocardiac failure. They reviewed the literature and found 126 reported cases which ended fatally. Since their report, Kerwin has added five cases and Hill, one case.

Etiology: In all patients the cardiac and respiratory embarrassment has resulted from a deformity of the spine and/or thorax, which caused a decrease in volume and in expansion of the thoracic cage. The deformities are classified as scoliosis, kyphosis, lordosis, kyphoscoliosis, and pectus excavatum or carinatum. The etiology of the deformity is not always obvious. Six of Chapman's 12 cases were caused by poliomyelitis and three others probably resulted from poliomyelitis. He postulated that poliomyelitis may always have been the chief cause of the deformities, though it may not have been recognized as such. Hill's case was the result of a poliomyelitis deformity. However, of Kerwin's five cases, two were caused by a tuberculosis of the spine, one by osteoporosis, one by an old injury and one by congenital defects. Chapman lists poliomyelitis, congenital or hereditary defects, rickets and tuberculosis in order of importance as causal factors.

Incidence: The total number of reported cases is too small to admit of valid statistical evaluation. In Kerwin's review of 6,700 routine autopsies he found the incidence of pulmonocardiac failure to be approximately one in every 1,340 cases or .075%. However, it is probable that the syndrome occurs frequently in persons who have a significant deformity. The deformity usually develops during childhood, achieving its maximum effect by the time the patient has attained full growth. Occasionally a deformity is present from birth. Severe chest deformities occur more frequently in males, and of the 126 cases reviewed by Chapman et al., the kyphoscoliotic curvature was to the right in all but 15. In 79 cases in which the autopsy material was adequate for study the average age at death was 30 years. The average age at death in five cases reported by Kerwin was 53 years.

Clinical Features: (a) Symptoms. The outstanding symptom in severe deformity of the chest is dyspnea, usually present for many years. However, the patient is able to carry on normal or only moderately restricted activity until the relatively sudden appearance of severe paroxysmal dyspnea, nocturnal dyspnea, weakness, palpitation or fainting which mark the onset of the terminal pulmonocardiac failure. Cough and epistaxis may occur and susceptibility to respiratory infections is increased. A definite sensitivity to morphine has been noted. The patient frequently gives a history of having to assume an unusual position in order to obtain partial relief of his dyspnea during an attack. In one of Chapman's cases, as in the present authors', this consisted of getting on the hands and knees. This behavior may be mistaken for a psychoneurotic manifestation.

(b) Signs. On physical examination the patients are small, frail and dyspneic with abdominal breathing predominating, and in the terminal stage are in severe respiratory distress. Tachycardia is a frequent finding, as is accentuation of the pulmonary second sound. Murmurs are rare and when present are of doubtful significance. The blood pressure is normal except for occasional elevation of the diastolic pressure. Cyanosis may be present but this is usually a late sign. Clubbing is absent. Rales may be the only signs of congestive heart failure, though peripheral edema may occur.

Because of the chest deformity cardiac enlargement may be difficult to determine by roentgenogram. The ECG may show right axis deviation but is usually normal except for a sinus tachycardia. Arrhythmias seldom are found. Polycythemia is not a feature of the disease. Routine laboratory studies are normal.

Autopsy Findings: Right ventricular hypertrophy and dilatation are present with occasional similar changes in the right auricle. Valvular lesions do not occur, nor is there any enlargement of the orifices of the pulmonary and tricuspid valves. The lungs often are small with focal pulmonary emphysema and atelectasis. Congestion and edema occur and terminal pneumonia is often present. One of the more striking findings is almost complete absence of any significant abnormality in the pulmonary vascular tree, either gross or microscopic. Thickening of the alveolar walls and pulmonary fibrosis are absent. Edema and passive congestion of the viscera are found but the remainder of the autopsy findings, except for the presence of the deformity, are not remarkable.

Mechanism: Decrease in respiratory capacity and thoracic volume are probably the chief factors responsible for the findings in pulmonocardiac failure. The studies by Chapman and his group of the respiratory physiology in their patients showed that the vital capacity may be reduced by one half or more with a consequent doubling of the ratio of the residual air to the vital capacity. The lungs are small as a result of the small thoracic volume and may actually be hypoplastic if the deformity occurs before the end of the growth period. In addition the deformity limits respiratory excursion. The secondary effects of these deficiencies include a decrease in the number and size of the pulmonary vessels available for gaseous transfer, and a decrease in the expansion of the pulmonary vessels which normally occurs during inspiration.[10,11] The logical result of this reduced pulmonary vascular bed, since it has been shown that the cardiac output is not changed in these patients,[7] would be an increased pulmonary pressure. Using the increased pulmonary second sound and the finding of right ventricular hypertrophy and dilatation as presumptive evidence, Chapman predicted that this would be the case, although no method was available for measuring the pressure of the lesser circulation directly, at the time of his paper. This was recently confirmed by Dexter. By venous catheterization he found the pulmonary artery and right auricular pressures to be 2 to 3 times normal in 3 cases of kyphoscoliosis.[12] There is some evidence to show that oxygen lack resulting from poor ventilation of the lungs may cause local constriction of pulmonary arterioles and precapillaries with an increase in the arterial resistance of the pulmonary circulation.[13]

The sequence of events, then, would seem to be: (1) a decrease in respiratory capacity; (2) an increase in pulmonary resistance and pulmonary arterial pressure acting over a long period of time; and (3) right ventricular hypertrophy and dilatation with eventual fatal cardiac and respiratory failure.

The case presented here demonstrated many of the typical findings of this disease; namely, thoracic deformity of severe degree, limited respiratory expansion, habitual dyspnea, cyanotic attacks and terminal cardiac failure. Autopsy revealed typical right ventricular hypertrophy and dilatation, small lungs with no marked vascular change, and moderate passive congestion of the viscera. Unusual features were: first, the presence of marked congenital spine and rib deformities with an extreme anomaly of the diaphragm; and second, the presence of dyspnea almost from birth with the terminal illness occurring in childhood, in contrast to the usual survival to 30 or more years of age. Neither of these has been described previously.

Summary

Pulmonocardiac failure is a clinical entity caused by severe spinal and thoracic deformity, usually ending fatally in early adult life.

Right ventricular hypertrophy and dilatation without any significant pulmonary vascular or interstitial fibrotic changes are prominent findings at autopsy.

The etiology, incidence, clinical manifestations and possible mechanism are discussed. A typical case occurring in childhood with certain unusual features is presented.

References

1. Bachman, M., Der Veranderungen des Innern Organe Bei Hochgradiger Skoliosen und Kyphoskoliosen, Stuttgart, Bibliothek Medica, 1899.
2. Klawansky, G., High-grade mechanical aortic stenosis due to kyphoscoliosis, Klin. Wchnschr. **4**:831, 1925.
3. Dedic, S., Kyphotic cardiopathy, Arch. d. mal. du coeur **23**:33, 1930.
4. Heidler, H., Kyphoscoliotic Heart und Gestation, Ztschr. f. Geburtsh. u. Gynek. **89**:294, 1925.
5. Frankenau, H., Does syndrome of lordosis heart exist? Schweiz. Med. Wchnschr. **66**:707, 1936.
6. Coombs, C. F., Fatal cardiac failure occurring in persons with angular deformities of chest, Brit. J. Surg. **18**:329, 1930.
7. Chapman, E. M., Dill, D. B., and Graybiel, A., Decrease in functional capacity of lungs and heart resulting from deformities of chest: Pulmonocardiac failure, Medicine **18**:167, 1939.
8. Kerwin, A. J., Pulmonocardiac failure as result of spinal deformity, Arch. Int. Med. **69**:560, 1942.
9. Hill, W. T., Scoliosis and cardiac failure, Am. Heart J. **37**:435, 1949.
10. Dupee, C., and Johnson, V., Respiratory changes in pulmonary vascular capacity, Am. J. Physiol. **139**:95, 1945.
11. Macklin, C. C., Length and width changes in pulmonary arterial system of rabbits in passing from stage of expiration to that of collapse as revealed by roentgenography, Dis. of Chest **11**:590, 1945.
12. Medical Grand Rounds, Am. Pract. **2**:764, 1948.
13. McMichael, J., Heart failure of pulmonary origin, Edinburgh M. J. **55**:65, 1948.

Spanish Abstract

Insuficiencia Pulmocardiaca. Reporte de un Caso

La insuficiencia pulmocardiaca es un sindrome causado por deformidades toracicas o de la columna vertebraral aisladas o combinadas. Este sindrome se caracteriza por dificultad respiratoria progresiva con insuficiencia cardiaca terminal. Los sintomas mas importantes son la disminución del vólumen toracico debido a las deformidades, dispnea persistente y aumento progresivo del ventriculo derecho. Además, existe un aumento de la resistencia pulmonar y presion arterial pulmonar. Los hallazgos patologicos demuestran la presencia de un pulmon pequeño, asi como una hipertrofia y dilatación del ventriculo derecho. Se nota la ausencia de alteraciones vasculares o de cambios fibroticos significantes en los pulmones.

Se presenta un caso de este sindrome ocurrido en un niño sufriendo de una severa deformidad congénita del diafragma y columna vertrebral, complicada con una insuficiencia respiratoria y cardiaca fatal.

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T WAVE CONTOUR IN THE PRECORDIAL LEADS DURING CHILDHOOD

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SHORTLY after the introduction of precordial leads, it was recognized that the criteria for normality of T wave contour in children differed from that in adults and that the presence of inverted T waves in the right precordial chest leads of children was a normal finding.[1-6] Diphasic, notched, or flattened T waves in these leads in children were also shown to represent normal transitional forms between the juvenile and adult complexes.[2-9] These normal diphasic T waves in the right chest leads are usually of the minus-plus variety with a steep slope between the two phases.[10] Whenever children have been studied in different age groups the increasing frequency of the adult type of T wave with advancing age has been evident.

Robinow, Katz and Bohning[4] attempted to account for the difference in T wave contour between children and adults on the basis of heart position, rotation, relative size and shape of the right and left ventricle, and relative proximity of the heart to the chest wall. Master, Dack and Jaffe[11] were unable to find any correlation between the T wave pattern and the anatomic position of the heart revealed by fluoroscopy and teleoroentgenography. Recently, Goldberger[12] has again stressed the importance of clockwise rotation of the heart on its longitudinal axis as a factor shifting the T wave transition further to the left in children.

Attempts have been made to establish the normal limits of the precordial V leads in children.[6-9, 12-15] To the author's knowledge, none of these reports has included an analysis of sufficient numbers of cases divided into age groups, to permit adequate determination of the normal precordial T wave contour, especially between the ages of 1 and 10 years. Therefore, a study was undertaken with reference to the T wave contour in children at different ages under normal and abnormal conditions.

MATERIAL

Records of 351 consecutive cases between 2 wk. and 20 yr. of age were selected from the recent files of the Heart Station and separated into groups depending upon the presence or absence of cardiovascular disease, or any disease or medication which might have been capable of affecting the cardiovascular system in these patients. The cases included in the abnormal series were diagnosed clinically as rheumatic fever, rheumatic heart disease or rheumatic stigmata in 44 instances, various types of congenital heart disease in 39, pyelonephritis or glomerulonephritis in 35, cor pulmonale or bronchial asthma in 11, sickle cell anemia or anemia of unknown etiology in 9; the remaining 26 included cases of emetine toxicity, pneumothorax, hypo- or hyperthyroidism, acidosis, ulcerative colitis, viral pericarditis, hypocalcemia, hypertension, pre-eclampsia or myocarditis.

In half the cases the standard, aV limb and precordial leads V4R, V1, V2, V4, V5 and V6 or V1 to V6 were recorded. In the remaining instances only the standard limb leads and V2, V4 and V5 had been obtained.

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Results

Table 1 shows the direction and character of the T wave in the precordial leads V2, V4 and V5 of the normal cases in the various age groups. Figure 1A to G illustrates some typical chest leads at various ages. In the younger ages no instance of an upright T wave was encountered in V2, nor was such a complex found in any of the chest leads further to the right during this age period. The youngest normal individual to show an

TABLE 1

Character of T Wave in Precordial Leads V_2, V_4 and V_5 in 187 Normal Cases

Age	# of Cases	V_2			V_4			V_5		
		Upright	Notched or Diphasic	Inverted	Upright	Notched or Diphasic	Inverted	Upright	Notched or Diphasic	Inverted
2 wk.–6 mo.	40	—	16	24	15	24	1	27	13	—
7 mo.–1 yr.	9	—	3	6	3	6	—	8	1	—
1	13	—	1	12	6	6	1	11	2	—
2	8	—	1	7	5	3	—	7	1	—
3	13	—	4	9	7	5	1	12	1	—
4	12	—	3	9	10	2	—	12	—	—
5	5	—	2	3	2	3	—	5	—	—
6	9	—	4	5	5	4	—	9	—	—
7	10	—	5	5	9	1	—	10	—	—
8	4	—	2	2	3	1	—	4	—	—
9	7	1	4	2	6	1	—	7	—	—
10	9	2	4	3	7	2	—	9	—	—
11	10	7	3	—	9	1	—	10	—	—
12	3	1	2	—	2	1	—	3	—	—
13	1	—	1	—	1	—	—	1	—	—
14	4	4	—	—	4	—	—	4	—	—
15	4	4	—	—	4	—	—	4	—	—
16	4	4	—	—	4	—	—	4	—	—
17	1	1	—	—	1	—	—	1	—	—
18	6	5	—	1	6	—	—	6	—	—
19	4	4	—	—	4	—	—	4	—	—
20	11	9	2	—	11	—	—	11	—	—

upright T wave in V2 was 9 years of age. From 2 weeks to 7 years of age, the T wave in V2 in the majority of cases was inverted; however, the frequency of notched and diphasic complexes increased as age 7 years was approached. The incidence of notched or diphasic complexes was greater under age 1 than between ages 1 and 4, the incidence of inverted T waves being more prevalent during this latter period. Between ages 8 and 14 years, inverted T waves in V2 were less frequent and upright complexes more commonly noted, the latter being even more prevalent after the age of 14. In one instance, at age 18, an inverted T wave was present and in two cases, at age 20, notched T complexes were observed in V2, all in females without cardiovascular disease.

Similar trends were noted in V4 but at earlier ages. While no inverted T waves were

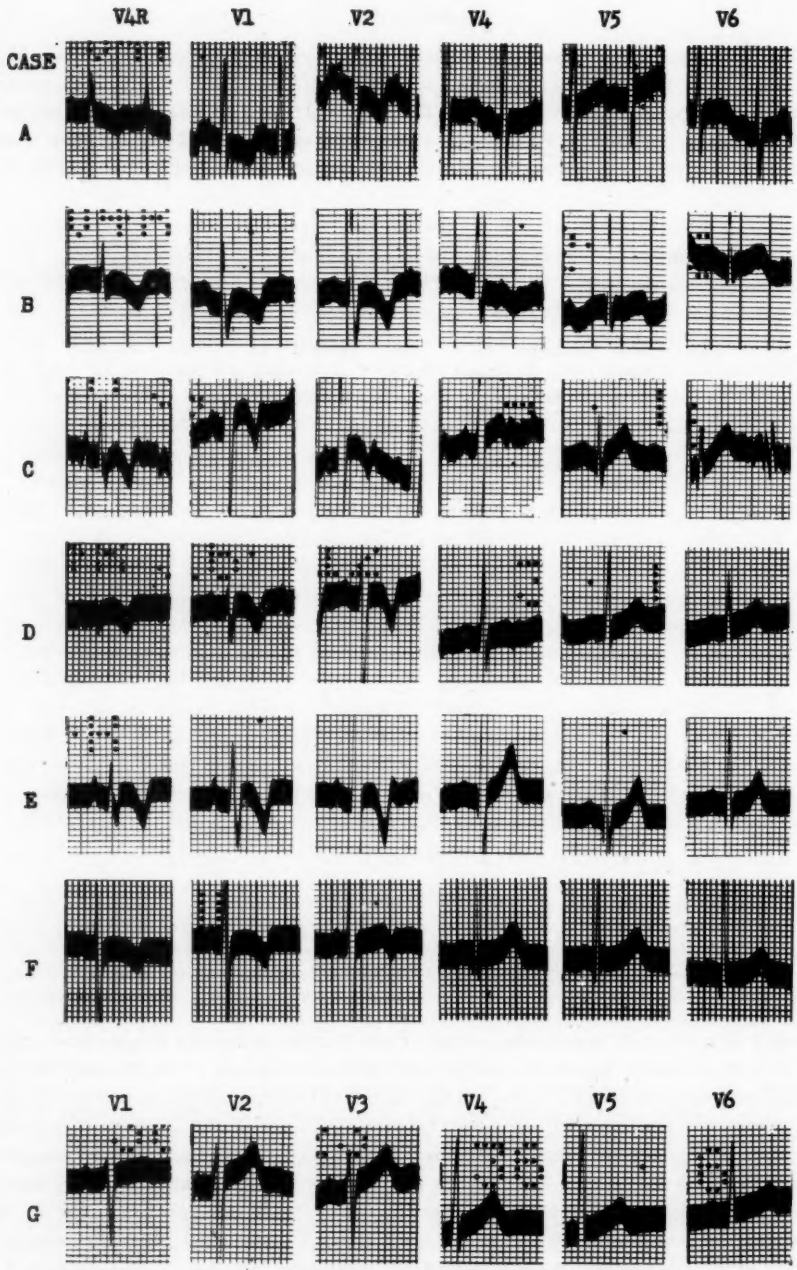

FIG. 1. Cases illustrative of normal T wave contour at various ages in childhood. Record A, from 4 wk. old child, shows inverted T wave in V4R and diphasic or notched complexes in remainder of

TABLE 2

CHARACTER OF T WAVES IN PRECORDIAL LEADS V_2, V_4 AND V_5 IN 164 ABNORMAL CASES

Age	# of Cases	V_2			V_4			V_5		
		Up-right	Notched or Diphasic	In-verted	Up-right	Notched or Diphasic	In-verted	Up-right	Notched or Diphasic	In-verted
2 wk.– 6 mo.	12	6	3	3	10	2	—	10	1	1
7 mo.– 1 yr.	7	1	2	4	2	3	2	3	2	2
1	6	2	2	2	3	2	1	5	1	—
2	6	3	2	1	4	2	—	4	1	1
3	12	2	3	7	6	4	2	7	4	1
4	8	1	5	2	5	3	—	6	1	1
5	5	—	3	2	2	3	—	4	1	—
6	9	1	1	7	5	1	3	9	—	—
7	8	—	2	6	2	4	2	7	—	1
8	7	1	2	4	4	1	2	6	—	1
9	6	2	2	2	5	—	1	5	1	—
10	5	2	—	3	3	2	—	4	1	—
11	15	6	6	3	14	1	—	14	—	1
12	16	6	4	6	12	4	—	14	1	1
13	6	3	2	1	4	2	—	6	—	—
14	10	5	2	3	8	—	2	9	—	1
15	3	3	—	—	3	—	—	3	—	—
16	6	2	3	1	5	—	1	6	—	—
17	2	2	—	—	2	—	—	2	—	—
18	4	3	1	—	2	2	—	1	3	—
19	4	—	1	3	4	—	—	4	—	—
20	7	2	1	4	3	1	3	5	1	1

found after age 3 in V4, they were frequently observed in V2 up to age 11, but only occasionally thereafter. Similarly, upright T waves in V4 were present as early as 2 weeks of age, while in V2 an upright T wave was noted only after the age of 8 years.

In V5, inverted T waves were not seen normally and diphasic complexes were not found after age 4. In lead V4, the oldest case to show diphasic T waves was age 12. In lead V2 such complexes were observed even at age 20 and occasionally they may persist in older persons.[16, 17]

The T wave transition zone in the multiple precordial leads moved to the right and

chest leads. Record B, from 5 mo. old child, shows progressively deeper inverted T waves from V4R to V2 and notched or diphasic, plus-minus, T waves in V4, V5 and V6. Record C, from 8 mo. old child, shows diphasic, minus-plus, T waves in V2 and V4 and upright T waves in V5 and V6. Record D, from child of 3 yr., has inverted T waves in V4R, V1 and V2, which become progressively deeper, and diphasic T wave in V4, and upright T wave in V5 and V6. In Record E, from child of 4 yr., T wave was inverted in V4R and V1, and mainly inverted in V2 with small upright phase following; upright T waves are seen in V4, V5 and V6, smaller in latter. Record F, from child of 5 yr., shows inverted T waves in V4R and V1, a triphasic T in V2, and upright T waves in V4, V5 and V6. For comparison, Record G, from young adult of 17 yr., shows normal upright T waves in all leads except V1 in which T is small and diphasic, plus-minus.

was found in fewer leads as the age increased, in spite of the frequent observation that the T wave became more deeply inverted as the transition zone was approached from right to left. Diphasic or notched complexes were not unusual in the region of change from an inverted to upright T wave irrespective of age or position of the transition zone itself.

Table 2 shows the nature of the T waves in leads V2, V4 and V5 in abnormal cases. Many of the patients included in this abnormal series had no demonstrable cardiovascular disease but suffered from a disease that might have been capable of involving the cardiovascular system. Many, therefore, had completely normal electrocardiograms. The over-all differences between the normal and abnormal group are thus not as great as might have

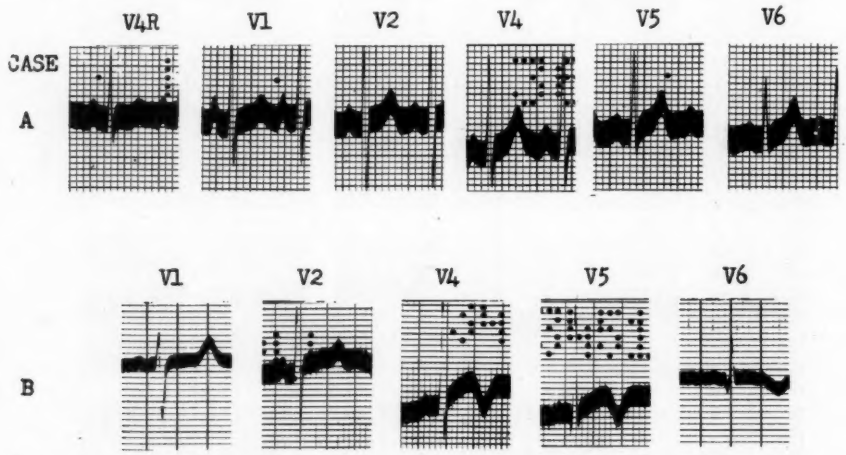

FIG. 2. Cases illustrative of abnormal T wave contour in presence of cardiac pathology. Record A is from 3 wk. old infant diagnosed clinically as tetralogy of Fallot. T wave is upright in all chest leads; adult appearance of these waves is apparent (contrast with A, B and C of Fig. 1) and is considered to be abnormal. Record B is from 14 yr. old male with acute pericarditis and illustrates abnormality of T wave, namely, reversal of normally expected sequence of T wave from V1 to V6.

been expected if all the cases in the abnormal series had had definite cardiac disease or abnormal ECGs.

Comparison of table 2 with table 1 reveals the most striking difference to be the presence, in the abnormal series, of a wide variety of T waves in all leads and at all ages, thus showing marked deviation from the orderly trends found in the normal series.

The presence of 17 cases of upright T waves in V2 of the abnormal group, under the age of 9, is striking since no such complexes were observed in V2 of the same age in the normal series. Of these 17 cases, 10 were clinically diagnosed as having some type of congenital heart disease (Fig. 2A), three as cardiovascular disease in the presence of pyelonephritis or glomerulonephritis, one as rheumatic heart disease, one as sickle cell anemia, one as toxic poisoning and one as cretinism. In the abnormal series, unlike the normal, it was not unusual to find the normal transition from inverted to upright T waves, in going from V4R to V6, unexpectedly reversed (Fig. 2B).

Discussion

In the normal series no instance of an upright T wave occurred in V2, or leads further to the right, between the age of 2 weeks and 9 years. Switzer and Besoain[9] and Tudbury and Atkinson[13] found no upright T waves in V2 in their normal cases between 1 and 5 years of age. Gros and Miller[18] have emphasized the presence of upright T waves in the right chest leads immediately after birth, which, in a few days become notched, diphasic or occasionally inverted. Because of the absence of an upright T wave in a total of 123 normal cases, in the present series, between 2 weeks and 9 years of age, and its appearance in 17 of the 80 abnormal cases under the age of 9, it would seem that an upright T wave in the right precordial leads, V4R to V2, might be considered abnormal in this

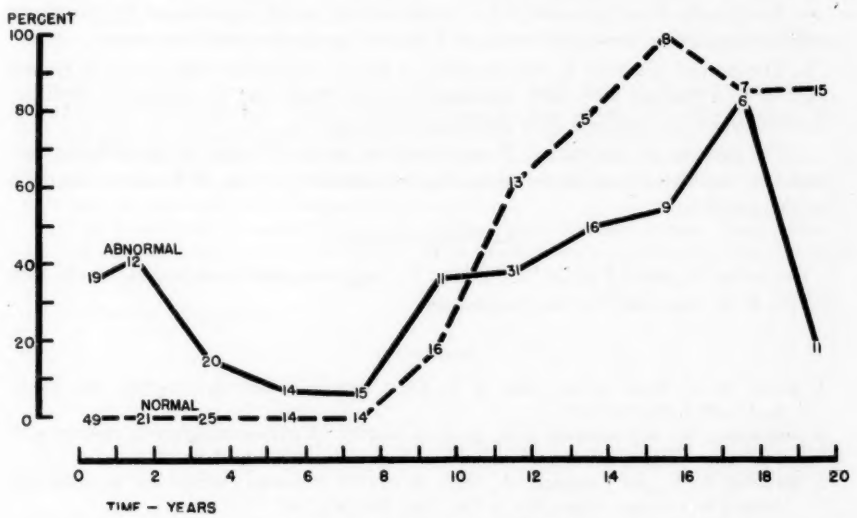

Chart 1. Diagram showing frequency distribution of upright T waves in V2. Percentage of upright T waves in V2 is represented by solid line for abnormal and broken line for normal cases. Number given at points along each line represent number of cases in each age group. It is apparent that under age of 9 yr. upright T wave in V2 may be considered abnormal until proved otherwise.

group. At least, it should be so considered until other diagnostic means have ruled out cardiac disease. This difference is clearly seen in chart 1.

In accord with Suarez and Suarez,[15] normally the present investigator did not observe inversion of the T wave in V5 or V6. However, Battro and Mendy[8] have reported inverted T waves as far to the left as V6 in normal children under the age of 2 years. An inverted T wave in V5 or V6 should be considered as suspicious at any age and should be viewed as abnormal until proved otherwise. Inverted T waves in V4 in patients over the age of 3, and diphasic or notched complexes in V4 or V5 after the age of 12 and 3, respectively, should likewise be viewed with suspicion. Of course, notched or diphasic complexes are expected in the transition zone.

A reversal or interruption in the normally expected sequential change of direction of

the T wave from the right to left precordial leads is definitely abnormal in children.

Explanations for the differences in the precordial T wave between children and adults has been attempted, but as yet none of them is definitely established.

Summary

The T wave in the precordial V leads was studied in 187 normal children and young adults in the age range of 2 weeks to 20 years and in 164 individuals of like age with cardiovascular disease or with disease or medication capable of affecting the cardiovascular system.

On the basis of this analysis correlated with a survey of the literature, it is concluded that:

a. An upright T wave in lead V2 or leads further to the right should be considered abnormal in children between 2 weeks and 9 years of age until proved otherwise.

b. The normal sequence in the direction of the T wave from V4R to V6 is from a negative to a positive wave with transitional forms which may be notched or diphasic. The reversal of this pattern is to be considered abnormal.

c. The presence of unexpected T wave contours in specific leads at the different ages should be considered as evidence demanding re-examination of the ECG and of the child for abnormalities.

Acknowledgment

The author is grateful to Dr. L. N. Katz for suggesting this study and to Dr. A. Pick and Dr. R. H. Rosenman for their suggestions.

References

1. Master, A. M., Dack, S., and Jaffe, H. L., Chest leads in normal children, Proc. Soc. Exper. Biol. & Med. **32**:1529, 1935.
2. Rosenblum, H., and Sampson, J. J., Study of lead IV of electrocardiogram in children with especial reference to direction of excursion of T wave, Am. Heart J. **11**:49, 1936.
3. Messeloff, C. R., and Pomerantz, A., Study of lead IV in normal children and in ambulatory children with cardiac disease, Am. J. Dis. Child. **53**:1485, 1937.
4. Robinow, M., Katz, L. N., and Bohning, Anne, Appearance of T wave in lead IV in normal children and in children with rheumatic heart disease, Am. Heart J. **12**:88, 1936.
5. Dwan, P. F., and Shapiro, M. J., Four lead electrocardiogram of children, Am. J. Dis. Child. **54**:265, 1937.
6. Ash, R., Precordial leads in childhood, Am. J. Dis. Child. **70**:277, 1945.
7. Littman, D., Persistence of juvenile pattern in precordial leads of healthy adult Negroes, with report of electrocardiographic survey on 300 Negro and 200 white subjects, Am. Heart J. **32**:370, 1946.
8. Battro, A., and Mendy, J. C., Precordial leads in children, Arch. Int. Med. **78**:31, 1946.
9. Switzer, J. L., and Besoain, M., Electrocardiograms of normal children, Am. J. Dis. Child. **79**:449, 1950.
10. Katz, L. N., Electrocardiography, ed. 2, Philadelphia, Lea & Febiger, 1946.
11. Master, A. M., Dack, S., and Jaffe, H. L., Precordial lead of electrocardiogram of normal children, Am. J. Dis. Child. **53**:1000, 1937.
12. Goldberger, E., Significance of downward T waves in precordial leads of normal children, Am. J. Dis. Child. **71**:618, 1946.
13. Tudbury, P. B., and Atkinson, D. W., Electrocardiogram of 100 normal infants and young children, J. Pediat. **36**:466, 1950.
14. Dunning, M. F., and Kuttner, A. G., Standard, unipolar limb and precordial leads in children and adolescents with inactive rheumatic fever, Am. J. Dis. Child. **77**:610, 1949.

15. Suarez, R. M., and Suarez, R. M., Jr., T wave of precordial electrocardiogram at different age levels, Am. Heart J. **32**:480, 1946.
16. Rosenman, R. H., and Reynolds, R. W., Transition zone in precordial electrocardiograms from multiple sites, to be published.
17. Rosenman, R. H., Silber, E. N., Katz, L. N., and Shorr, B., Value of aV limb leads and of V chest leads (V4R-V7) in routine clinical electrocardiography, Am. Heart J., to be published.
18. Gros, G., and Miller, R., Electrocardiogram in normal children from birth to five years, to be published.

SPANISH ABSTRACT

El Contorno de la Onda T en las Desviaciones Precordiales en Niños

La onda T en las desviaciones precordiales fué estudiada en 187 niños y adultos jovenes normales cuyas edades variaron entre dos semanas y veinte años de edad y en un grupo de 164 individuos de edades similares con enfermedades cardiovasculares, o con enfermedades o medicamentos capaces de afectar el sistema cardiovascular.

Basándose en el análisis de éste estudio y en el "survey" de la literatura, el autor concluye:

a) Una onda T positiva en V2 o en desviaciones mas hacia la derecha, debe considerarse anormal en niños entre dos semanas y nueve años de edad hasta que lo contrario sea probado.

(b) La evolución normal en la dirección de la onda T partiendo de V4R a V6 es de una onda negativa a una positiva con ondas transicionales que pueden ser difasicas o "notched." Lo contrario en la dirección de esta onda debe considerarse anormal.

(c) La presencia de una onda T inesperada en desviaciones especificas durante edades diferentes debe considerarse como evidencia demandativa de un nuevo exámen electrocardiografico y exámen del paciente por posibles alteraciones.

29th Street and Ellis Avenue

CIRCULATING EOSINOPHILS IN CHILDREN IN HEALTH AND DISEASE

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AT THE present time the role of the adrenal cortex in disease is the subject of intensive investigation. The response of the adrenal gland to various forms of stress may be studied by measurement of changes in the circulating eosinophil count. The studies of Thorn et al.[1] have provided a simple clinical method for determining the adrenocortical reserve in normal and Addisonian patients following the administration of ACTH. The decrease in the number of circulating eosinophils following test doses of epinephrine and insulin has also been used as an index of adrenocortical function.[2-4] In the majority of these studies the determination of the adrenocortical reserve has been done in adults.

The present report is concerned with a comparison of the circulating eosinophil counts in a series of children including those in apparent health as well as those experiencing a variety of febrile and nonfebrile illnesses. In addition, the response of the circulating eosinophils to test doses of ACTH, epinephrine and insulin was studied.

MATERIAL AND METHODS

Venous or capillary blood may be used for measuring the circulating eosinophils. In the author's experience finger-tip blood was found to be practical and satisfactory. The eosinophil counts were determined using the Thorn modification of the Dunger method[5] in which the eosinophils are stained bright red with an acetone-eosin stain while the other leukocytes are almost colorless. The Randolph phloxin stain[6] may also be used.*

The white cell pipettes and special diluting fluid† are placed in a tray of cracked ice for 10 min. prior to use. Blood is drawn up to the 0.1 mark, the diluting fluid to the 1.1 mark. The pipette is shaken gently at once for 30 sec. and replaced in the tray. The 0.2 mm. depth Levy counting chamber with Fuchs Rosenthal linear markings is filled and the eosinophils counted in the 16 large squares on each side of the chamber after 3 min. The final count is calculated by multiplying the total count in each chamber by the factor 3.125 and the average value used. It has been found that in a series of 8 duplicate determinations, the filled pipette may be stored at —20° C. or in the ice compartment of the refrigerator for at least 1 wk. with no change in the number of circulating eosinophils. At least 5 min. should be allowed for thawing and the pipette again gently shaken for 30 sec. before filling the counting chamber. It has been found that when the refrigerator is opened frequently, storage is not satisfactory. Gentle shaking consists of 1 shake/sec. Thawing should be done at room temperature and not by applying heat; the pipette should still be cold after thawing, never warm.

The "ACTH test" was done in the postprandial state, the last food having been given at 7 p.m. on the day prior to the test. Finger-tip blood was taken at 9 a.m. and 4 hr. after the administration of ACTH.

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* In differential smears the eosinophil count is not satisfactory unless the original number of eosinophils is more than 10%.

† The diluting fluid contains 10 ml. of 2% aqueous eosin solution, 10 ml. of acetone diluted with water to 100 ml.

In patients experiencing a febrile illness, daily eosinophil counts were determined through the convalescent period. The "epinephrine test" and the "insulin test" were done under the same conditions as the "ACTH test" with the exception that in the "epinephrine test" a 3 hr. interval was used. In the "ACTH test," 25 mg. of ACTH was injected intramuscularly. In the "epinephrine test" 0.3 cc. of 1/1000 solution was injected subcutaneously. In the "insulin test" 0.25 units of insulin/kg. body weight was injected subcutaneously.

A total of 351 circulating eosinophil counts were done on 75 children observed in the Pediatric Pavilion of The New York Hospital:

(a) 18 healthy children.

(b) 29 patients with acute febrile illnesses including 19 with active carditis, 7 with acute infections, 2 with disseminated lupus erythematosis and 1 with acute myeloblastic leukemia.

(c) 3 patients with mild febrile illnesses.

(d) 12 patients with nonfebrile miscellaneous diseases including Cushing's syndrome, adrenogenital syndrome, mild hypopituitarism, diabetes mellitus, diabetes insipidus, postencephalitis disease, an extrathoracic abscess, retrolental fibroplasia, chronic hemolytic anemia, cervical spine tumor with spastic paraplegia, rheumatoid arthritis and chronic osteomyelitis.

(e) 10 patients with various allergies including 6 with eczema, 2 with pansinusitis and 2 with eosinophilia of unknown etiology.

(f) 3 patients were studied before and after surgery; 2 patients had tonsillectomies and 1 patient had a laparotomy.

Observations

The range of circulating eosinophils for the children in apparent health was 109 to 359, which is well within the range of 80 to 500 given by Thorn et al.[7] for their normal adults. The circulating eosinophil counts for the patients in the nonfebrile miscellaneous disease group and those with mild febrile illnesses also fell within the normal range, being 84 to 599 and 170 to 341, respectively. In the miscellaneous disease group the patients were all chronically ill and about half the patients had endocrine disorders. From these results it would appear that in the presence of chronic stress some degree of adaptation, in accordance with Selye's hypothesis, has taken place. The normal range in the circulating eosinophils in mild febrile illnesses may be attributed to the absence of severe stress in these patients.

The range in the initial counts for the children experiencing acute febrile illnesses was 0 to 97. In chart 1 the response of the circulating eosinophils in three of these patients is presented. It will be seen that the drop in temperature as the patients improved under antibiotic therapy was paralleled by a rise in circulating eosinophils to normal levels.

It is of interest that in 1907 the French investigator Lams[8] stated that the eosinophils were an "index of convalescence." The prognostic significance of the circulating eosinophil counts in severe illness is illustrated by curve III in which the eosinophil counts in a patient with pneumococcic meningitis are presented. It may be noted that at the onset the eosinophil count was 0, indicating a normal adrenocortical reserve. This patient made a striking clinical recovery following penicillin-aureomycin therapy. In marked contrast is a recent report by Faloon et al.[9] of a patient with Waterhouse-Friderichsen syndrome. Here, the initial count was 21, rising to 90 on the second hospital day, indicating a poor adrenal response to severe stress. These investigators gave supportive therapy with adrenocortical extract which lowered the eosinophil count to 6. It would, therefore, seem of prognostic importance to determine the circulating eosinophil count routinely in patients with acute febrile illnesses.

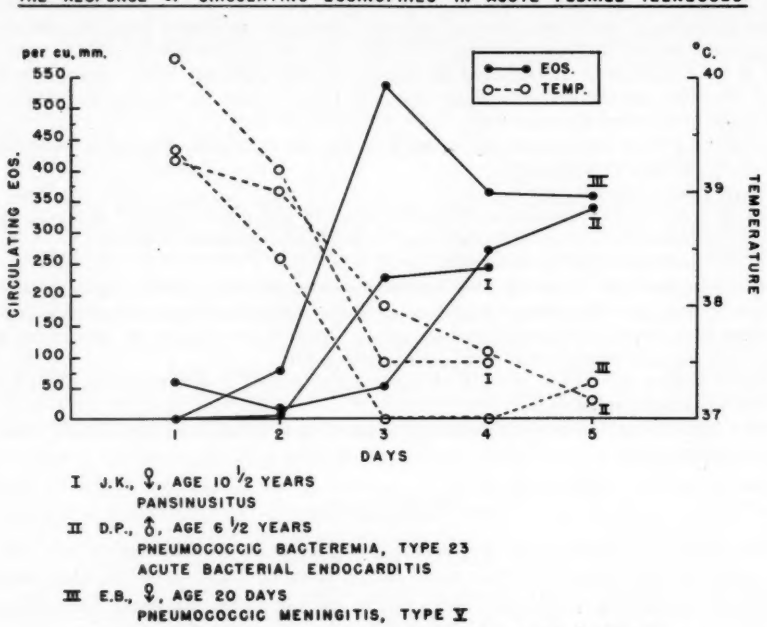

CHART 1. Response of circulating eosinophils in acute febrile illnesses.

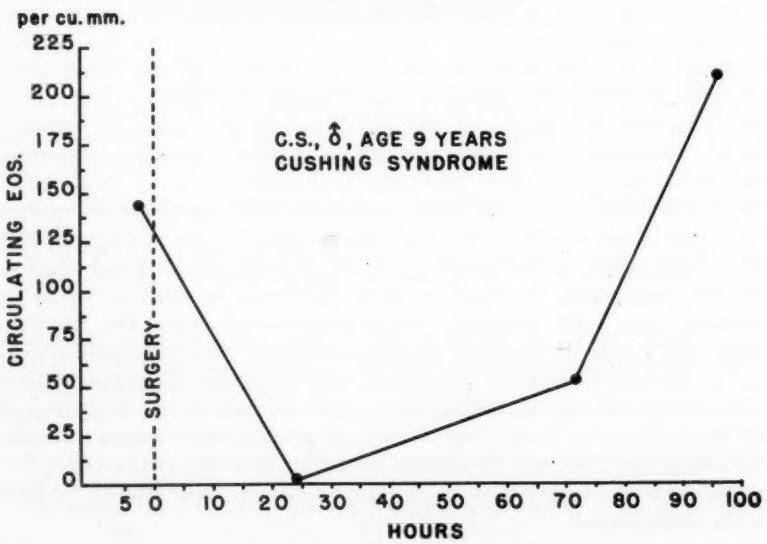

CHART 2. Circulating eosinophils before and after surgery.

Chart 2 illustrates the changes in the circulating eosinophils in a patient before and after laparotomy. The expected drop in the circulating eosinophils in patients with normal adrenocortical reserve was obtained 24 hours after surgery. The "ACTH test" on this patient before surgery was normal, indicating that he was a good surgical risk. As Roche et al.[10] have recently stated, this finding is considered a good prognostic index. These authors also recommend the use of the "ACTH test" prior to surgery in order to evaluate the adrenocortical reserve before the severe stress of operation.

The range of the circulating eosinophil counts for the group of children with allergic

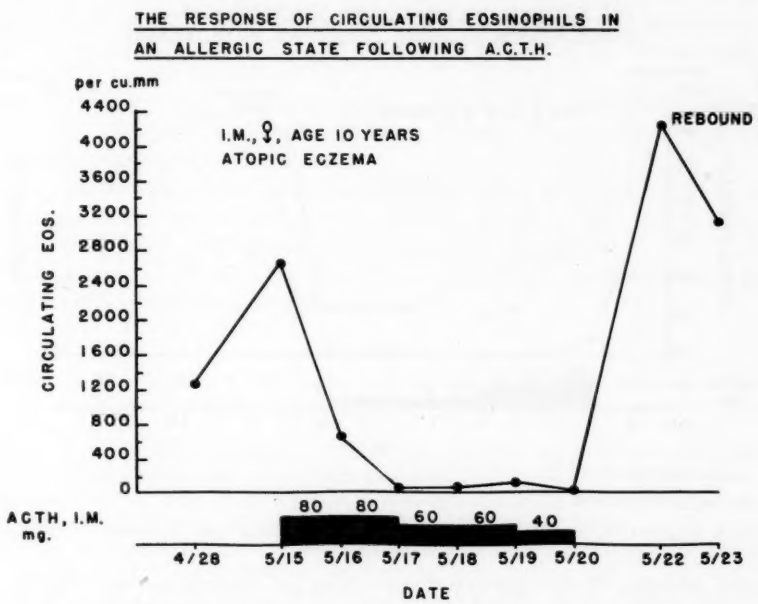

CHART 3. Response of circulating eosinophils in allergic state following ACTH.

manifestations was 393 to 2665. These values are well above the normal range, as would be expected. The changes in the circulating eosinophil count in a child with acute atopic eczema treated with ACTH are shown in chart 3. It will be seen that this patient exhibited the characteristic high eosinophil count observed in allergic states. Following administration of ACTH for 5 days there was a precipitous drop in circulating eosinophils which reached a low level of 18 but never dropped to 0.

It has been considered that there is an antagonism between the factors controlling the eosinophilia in allergic disorders and the normal factors responsible for the decrease in circulating eosinophils.[1,2] This is reflected in the irregular response of the circulating eosinophils in allergic patients treated with ACTH or cortisone, or under stress. It is of interest that the eczema disappeared during therapy but returned gradually after therapy was discontinued.

In a previous publication,[11] the response of the circulating eosinophils four hours following the administration of ACTH 25 mg. was shown for a group of 23 children, including normal subjects and patients with miscellaneous illnesses, as well as active and

inactive rheumatic fever. The per cent decrease in total circulating eosinophils was of the same order of magnitude in all groups, the range being from −30 to −100. These observations are comparable to those reported by Thorn et al. for adults. It is apparent that the adrenocortical reserve as determined by this test is normal in rheumatic children. In marked contrast are the observations of Thorn et al.[1] in Addison's disease. They observed a decrease in the eosinophils following the administration of ACTH of −4% or less. Almy et al.[4] have recently reported comparable observations following the subcutaneous injection of epinephrine 0.5 cc. in Addisonian patients. The present author's results

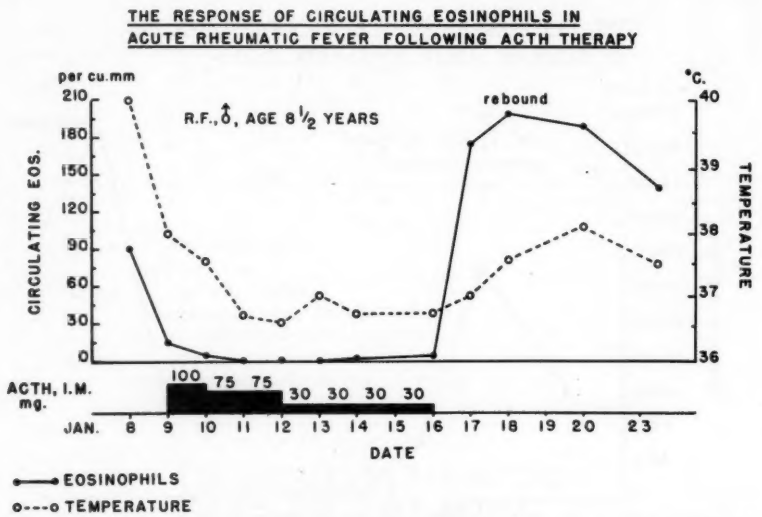

CHART 4. Response of circulating eosinophils in acute rheumatic fever following ACTH therapy.

in eight children with miscellaneous diseases using the "epinephrine test" and the "insulin test" are comparable to the results of Laragh and Almy[3] and Recant et al.[2] with adults, the drop in circulating eosinophils ranging from −53% to −69%. The practical application of these tests in differential diagnosis, particularly in patients in whom diminished adrenocortical reserve is suspected, is obvious.

Chart 4 illustrates the response of the circulating eosinophil count to the administration of ACTH for seven successive days in a patient with acute rheumatic fever. It may be seen that the eosinophils dropped precipitously to 0 and remained there during therapy, rising above the normal level 24 hours after ACTH was discontinued. The low initial circulating eosinophil count is a characteristic response which has been observed in patients with acute febrile illnesses who have a normal adrenocortical reserve. The level of the circulating eosinophil count is used as an index to the adequacy of ACTH dosage.[12] It is of interest that this patient made a spectacular recovery and was well within two weeks.

COMMENT

The mechanism responsible for the decrease in the eosinophil count following stress is obscure. However, the decrease apparently reflects the adequacy of the adrenocortical

reserve. It has been shown in this presentation and by other investigators that the determination of the circulating eosinophil count is of diagnostic and prognostic significance. It appears that the circulating eosinophil count, provided that it is done under carefully controlled conditions, is a simple, practical clinical test of adrenocortical reserve.

Summary

A total of 351 circulating eosinophil counts were done on 75 children.

The range of circulating eosinophils for 18 normal children was 109 to 359.

In 12 patients with nonfebrile miscellaneous diseases the circulating eosinophil counts ranged from 84 to 599, and in three patients with mild febrile illnesses, from 170 to 341. A possible explanation for the fact that these counts fell within the normal range was discussed.

In 29 patients with acute febrile illnesses the initial circulating eosinophil counts ranged from 0 to 97. Serial counts during convalescence on three of these patients are presented and the prognostic significance discussed.

In 10 patients with various allergic manifestations there was a range of 393 to 2665. Serial counts on one case of acute atopic eczema treated with ACTH are presented.

Serial counts on one patient before and after laparotomy are presented.

Results of the "ACTH test," the "epinephrine test" and the "insulin test" on a group of children with miscellaneous diseases are presented.

References

1. Thorn, G. W., Forsham, P. H., Prunty, F. T. G., and Hills, A. G., Response of pituitary adrenocorticotropic hormone as test of adrenal cortical insufficiency, J.A.M.A. **137**:1005, 1948.
2. Recant, L., Hume, D. M., Forsham, P. H., and Thorn, G. W., Studies on effect of epinephrine on pituitary-adrenocortical system, J. Clin. Endocrinol. **10**:187, 1950.
3. Laragh, J. H., and Almy, T. P., Reduction in circulating eosinophils following insulin, epinephrine and surgical operations, Proc. Soc. Exper. Biol. & Med. **69**:499, 1948.
4. Almy, T. P., Laragh, J. H., and Cohen, E. J., Response of circulating eosinophils to epinephrine as index of adrenal cortical function, New York Med. **6**:16, 1950.
5. Forsham, P. H., Thorn, G. W., Prunty, F. T. G., and Hills, A. G., Clinical studies with pituitary adrenocorticotropic hormone, J. Endocrinol. **8**:15, 1948.
6. Randolph, T. G., Blood studies in allergy. I. Direct counting chamber determination of eosinophils in propylene-glycol-aqueous-stain, J. Allergy **15**:89, 1944.
7. Roche, M., Hills, A. G., and Thorn, G. W., Levels of circulating eosinophils and their response to ACTH in surgery: Their use as index of adrenal cortical function, Proceedings of the First Clinical ACTH Conference, edited by J. R. Mote, Philadelphia, The Blakiston Company, 1950.
8. Lams, H., L'eosinophile considérée comme moyen de pronostic, Compt. rend. Soc. de Biol. **62**:489, 1907.
9. Faloon, W. W., Reynolds, R. W., and Beebe, R. T., Use of direct eosinophil count in diagnosis and treatment of Waterhouse-Friderichsen syndrome, New England J. Med. **242**:441, 1950.
10. Roche, M., Thorn, G. W., and Hills, A. G., Level of circulating eosinophils and their response to ACTH in surgery, New England J. Med. **242**:307, 1950.
11. Hain, Katharine, and Wilson, May G., Immunologic and biochemical studies in infants and children with special reference to rheumatic fever. VIII. Response to pituitary adrenocorticotropic hormone (ACTH), Pediatrics **4**:579, 1949.
12. Randolph, T. G., and Rollins, J. P., Eosinophil observations in adrenocorticotrophic hormone (ACTH) therapy, Proceedings of the First Clinical ACTH Conference, edited by J. R. Mote, Philadelphia, The Blakiston Company, 1950.

SPANISH ABSTRACT

El Conteo Total de Eosinófilos en Niños Sanos y Enfermos

Un total de 351 conteos de eosinófilos de la sangre fueron hechos en 75 niños. Los limites de los eosinófilos en 18 niños normales variaron entre 109 y 359 por milimetro cubico de sangre. En doce niños con enfermedades diversas pero afebriles, el número de eosinófilos varió entre 84 y 599 y en tres pacientes con enfermedad ligera febríl el número de eosinófilos osciló entre 170 y 341.

En 29 pacientes con enfermedades febriles el conteo inicial de los eosinófilos varió entre 0 y 97. Conteos seriados fueron realizados durante la convalecencia en tres de estos pacientes y la significancia pronóstica es discutida.

En 10 pacientes con manifestaciones alergicas diversas el promedio de los eosinófilos osciló entre 393 y 2665. El autor presenta data de conteos seriados de eosinófilos en un niño con eczema atopico agudo tratado con ACTH y de un paciente antes y después de una laparotomia.

Se presentan los resultados del "ACTH test," "epinephrine test" y "insulin test" en un grupo de niños padeciendo de enfermedades diversas.

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GASTROINTESTINAL LESIONS IN ACUTE BULBAR POLIOMYELITIS

Report of Five Cases with Recovery in One

By CHARLES D. COOK, M.D., JOHN R. HARTMANN, M.D., STANLEY J. SARNOFF, M.D., AND WILLIAM BERENBERG, M.D.

Boston

DURING the 1949 poliomyelitis epidemic in Massachusetts, a patient with acute bulbo-encephalitic poliomyelitis and associated severe gastrointestinal hemorrhage with recovery was treated at the Boston Children's Hospital. A review of the literature shows two recent reports[1-3] dealing with esophageal perforation in bulbar poliomyelitis and a review of the autopsy files of this hospital produced three instances of fatal poliomyelitis with perforations of the upper alimentary canal. In addition a patient with bulbar poliomyelitis and gastrointestinal bleeding without perforation but with a fatal outcome was treated here in 1949. Such gastrointestinal complications are apparently more common than previously considered and form the basis of this report. Their possible etiology is discussed.

CASE REPORT

Case 1. B.P., a 9 4/12 yr. old boy, entered the Boston Children's Hospital with a history of fever and malaise for 4 days and a nasal voice and stiff neck for 24 hr. Physical examination showed an acutely ill child with temperature 40°C., respirations 34, and pulse 80/min. Blood pressure was 148 systolic/102 diastolic. Respirations were regular and normal and the child was oriented and alert. He had a left lower facial weakness, nasal voice, absent gag reflex, paralysis of the soft palate, rigidity of the back and neck, and marked limitation of straight leg raising. Examination of the cerebrospinal fluid revealed 190 WBC/mm.^{3} with 72% mononuclear cells, 40 mg./100 cc. protein and normal sugar. Following admission to the hospital he rapidly became worse (see chart 1), requiring tracheotomy and treatment with the electrophrenic respirator* on the second day. The latter was necessitated by the onset of irregular, shallow respirations accompanied by an increase in pulse rate and by severe encephalitic signs. The boy was semicomatose, responding to painful stimuli only by withdrawal of the part affected. His dependence on the electrophrenic respirator was demonstrated by the grossly inadequate ventilation (Fig. 1), the onset of restlessness and the increase in blood pressure as soon as electrophrenic respiration was withdrawn. Conversely, as soon as regular respiration was re-instituted by the stimulator, he would become quiet and his blood pressure would return to normal.

After 6 days on the electrophrenic respirator, the patient was transferred to a Drinker-type chest respirator. During the third hospital week, the patient was able to breathe adequately without artificial aid.

On the seventh day of his disease, or his second hospital day, he had coffee-ground vomitus and 3 small tarry stools. Six days later, while apparently recovering, he suddenly presented the signs and symptoms of shock. Whole blood transfusions were initiated. Shortly thereafter he began to pass grossly bloody stools. Abdominal and rectal examination at that time revealed no abnormal findings

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* The use of the electrophrenic respirator in this case by Dr. S. J. Sarnoff and co-workers is included in a separate report.[4]

and there was no pain associated with the bleeding. There was no evidence of blood dyscrasia and no response to vitamin K (hykinone Rx) parenterally. In the hope that parasympatholysis might reduce the hemorrhage, atropine was given for 2 days without apparent effect. The bloody stools continued for 6 days. He required daily transfusions up to 1200 cc. of whole blood in addition to albumin and saline solutions to maintain an adequate circulatory status. First gavage feedings were started on the 16th day of the disease and an ulcer regime with milk and aluminum hydroxide was given in an effort to reduce irritation at the bleeding point. No previous intubation had been

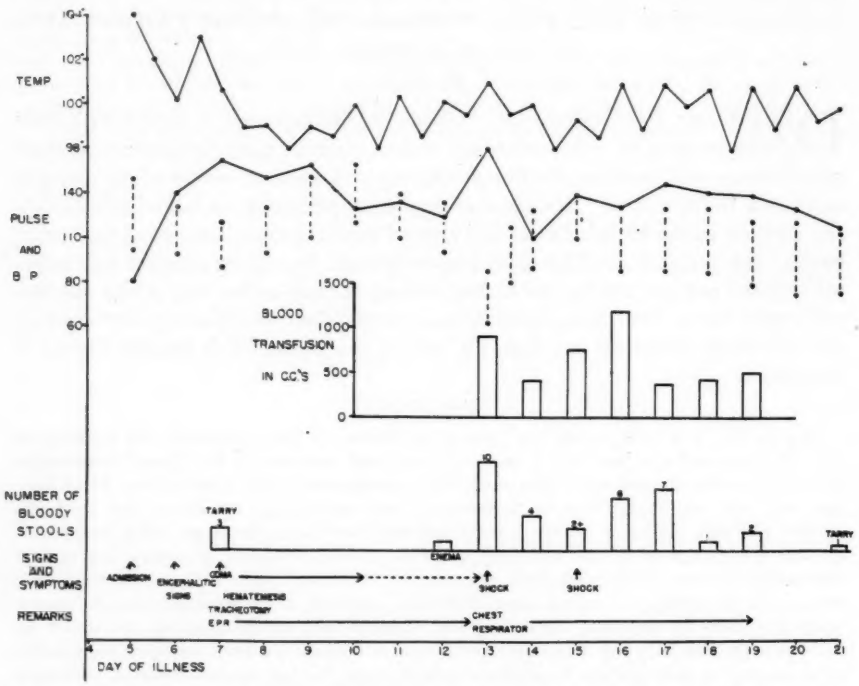

CHART 1. Clinical chart showing relation of gastrointestinal hemorrhage to course of disease and amount of administered whole blood required to maintain circulation.

used which might have precipitated the hemorrhage. At no time after the second hospital day was there any vomiting. On the 21st day of his disease the patient began to have formed, guaiac negative stools which persisted. Barium enema and gastrointestinal series on the 39th and 41st day of his illness revealed no abnormalities. (His serious condition had precluded such investigations prior to that time.)

Nine weeks after admission the patient was transferred to his local hospital. At that time he had marked weakness of the anterior neck muscles, some mild dysphagia, and moderate peripheral weakness. At the time of this report (4 mo. later), he had regained 4.1 kg. and was able to swallow all types of food, although coordination of sneezing and coughing was less than normal. Some neck weakness remained but was not severe enough to keep the patient from normal participation in all activities. At that time he had no abdominal pain and no further evidence of intestinal bleeding.

A review of 54 fatal cases of acute poliomyelitis with postmortem examination at the Children's Hospital since 1916 revealed gross lesions of the gastrointestinal tract in three

instances. These patients had had severe bulbar involvement and all showed small perforations of the lower third of the esophagus, but only one had had hematemesis before death. A fourth bulbar patient, dying during the 1949 epidemic, had premortem gastrointestinal bleeding.

Case Histories

Case 2. E.M., a 9 yr. old boy, entered the hospital with a 3 day history of fever, headache and stiff neck. Physical examination showed slight cyanosis, difficult respirations, paralysis of the diaphragm and intercostal muscles. The cerebrospinal fluid contained 270 WBC/mm.^{3} with 85% mononuclear cells and gave a strongly positive globulin reaction. He required the pulmotor on several occasions and, 2 hr. before death, on the second hospital day, vomited chocolate-colored bloody material. Postmortem examination showed 2 linear perforations of the lower third of the esophagus, each 2 by 0.5 cm. in size. The openings had small, sharp nonindurated margins, 2 and 5 cm. above the diaphragm, respectively. The adjacent areas were thin and friable. The ruptures were interpreted as being premortem in character.

Case 3. M.M., a 3 yr. old girl, was admitted to the hospital because of listlessness for 2 days

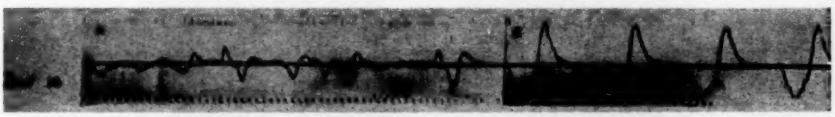

Fig. 1. Pneumotachograms (tracheal air flow patterns) in Case 1 during (a) spontaneous respiration and (b) electrophrenic respiration. Inspiration is down, expiration up. Inspiratory tidal volume is proportional to area below base line.

with headache, fever, stiff neck and vomiting of clear material. On physical examination the temperature was 40.5°C. There was a right palatal, a pharyngeal and a left facial weakness. The cerebrospinal fluid contained 193 WBC/mm.^{3} with 76% mononuclear cells and showed a strongly positive globulin test. The child rapidly developed more severe signs with irregular respirations, intermittent cyanosis and a terminal rise in fever on the third hospital day to 42.2°C. Postmortem examination showed esophagomalacia with a small perforation into the right pleural cavity. The mucosa of the esophagus was injected. There was no gross blood in the gastrointestinal tract.

Case 4. J.M., an 11 yr. old boy, entered the Children's Hospital with progressive fever, difficulty in swallowing and breathing for 1 wk. The cerebrospinal fluid showed 150 mononuclear cells/mm.^{3} The patient was placed in a respirator and developed increasing encephalitic signs with stupor, cyanosis, peripheral vascular collapse and a terminal fever of 41.6°C. He died on the day following entry. An autopsy examination showed a 3 cm. long perforation of the esophagus at the junction of the middle and lower thirds. The edges were indefinite and frayed without evidence of organization but with a few polymorphonuclear cells already present. The mucosa of the lower ileum was congested, most marked proximal to the ileocecal valve (see Fig. 2). There was also definite evidence of medullary involvement of the brain stem with hemorrhage and congestion.

Case 5. R.H., a 10 yr. old boy, entered the Children's Hospital because of fever, malaise, drowsiness and stiff neck for 2 days. On admission the temperature was 40°C., pulse 128 and respiration 20. The child had a stiff neck, right palatal and some peripheral weakness and signs of early encephalitis. The latter symptoms progressed until the fourth hospital day when he became comatose and developed respiratory difficulty. A tracheotomy was attempted to provide a more adequate airway but the patient died during the procedure. Two and a half hours before death, the patient passed a tarry stool. At the time of postmortem examination, the large intestine was filled with guaiac positive tarry feces. Further examination showed multiple petechial hemorrhages in the ileum but no point of gross hemorrhage or ulceration.

Discussion

The occurrence of gastrointestinal perforation and/or hemorrhage in acute bulbar poliomyelitis is not rare but on the contrary has been seen by some observers with significant

frequency. Weinstein,[5] at the Haynes Memorial Hospital in Boston, had treated four patients during the 1949 epidemic with gastrointestinal pathology on postmortem examination which was similar to that seen at the Children's Hospital. Rundlett and co-workers,[6] at the Jersey City Medical Center, reported (out of a total of 160 patients admitted to that clinic with the diagnosis of poliomyelitis in 1949) seven patients, all of whom had bulbar poliomyelitis, with hematemesis ranging from coffee-ground vomitus to massive hemorrhage. At the same time, Wilson[7] in Ann Arbor had at least one patient with acute

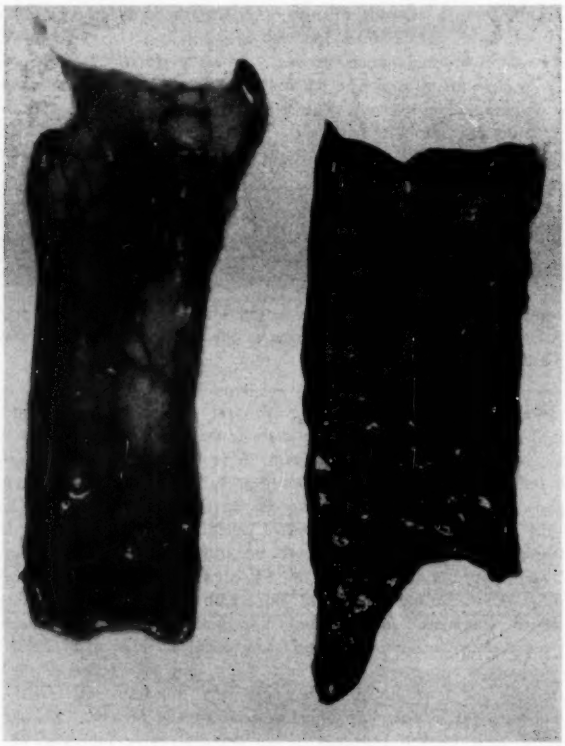

FIG. 2. Section of lower ileum from Case 4 showing hemorrhagic mucosa (right) compared with normal portion of ileum (left) in same patient.

bulbar poliomyelitis who had strongly guaiac positive stools for three days. A review of the literature reveals a recent report by Erskine and co-workers[2] of two young adults with bulbar poliomyelitis in whom multiple ulcerations of the esophagus with perforation were demonstrated on postmortem examination. An earlier report by Heyde and Robinson[3] also described two cases of bulbar poliomyelitis with acute gastrointestinal perforation.

That the lesions are apparently not terminal or postmortem may be seen from the cases presented. In the present authors' experience, the so-called Rokitansky-Cushing ulcer in

the esophagus has been seen in such varied conditions as brain tumor, brain abscess and meningitis. In the latter condition esophageal ulceration has occurred when the entire process has been less than 24 hours in duration.

Cushing has postulated a relationship between damage to the midbrain and lesions in the gastrointestinal tract occurring in brain tumors and malignant hypertension.[8] He stated that "experimental lesions anywhere in the intracranial course of these fiber tracts (the cerebral sympathetics) . . . are prone to cause gastric erosions, perforations and ulcers. Intracranial injuries and disorders affecting these same basilar regions in the brain are known to be accompanied by ulcerative lesions of the upper alimentary canal." Although no microscopic study of the brains of the patients presented in this report was made other than to substantiate the diagnosis of poliomyelitis, it is possible that a similar relationship between damage to the basilar structures in the brain and lesions of the gastrointestinal tract occurs in acute bulbar poliomyelitis.

In the cases reported here, gastrointestinal perforation or hemorrhage has always been associated with respiratory center involvement and has not been seen with less severe bulbar poliomyelitis. Perhaps if the phenomenon is looked for routinely, this will not be true; however, it would seem probable that severe brain stem disease would be present when gastrointestinal lesions appear.

Gastric intubation has not played an etiologic role in the esophageal perforations reported in the present series. External trauma has also been absent unless the use of respirators could play an etiologic role. This latter factor does not seem important in view of the lack of gastrointestinal complications when the respirators are used for months or even years in convalescent poliomyelitis patients.

In Case 1 the possibility that the stimulation of the vagus nerve occurred during electrophrenic respiration and caused the intestinal hemorrhage has been considered. However, experimental observations[9] have shown that the vagus is not stimulated by the apparatus used since bradycardia does not accompany its use. Further, the first tarry stools observed in this patient occurred prior to the first use of the electrophrenic respirator.

The role of anoxia in the production of hemorrhages and perforation was also considered. In the experience of the Children's Hospital,[10] severe cyanosis in itself has not led to esophageal or gastric perforation. On the other hand, small bowel petechial hemorrhages may possibly be accounted for on the basis of anoxia. Case 5 represents a condition which may or may not be related to the Cushing or Rokitansky ulcers. In this case the gastrointestinal involvement consisted of petechial hemorrhage in the ileum. This ileal involvement was also seen in Case 4, in addition to the esophageal perforation. Clinically, the two types of gastrointestinal involvement (upper and lower alimentary tract) would be hard to differentiate, but the two may be quite different from an etiologic point of view.

Reflux of gastric contents into the esophagus causing esophageal erosion was also considered but again seemed unlikely in view of lack of pathologic confirmation on this point. As shown by Neuhauser and Berenberg,[11] chalasia was not associated with ulcerations. However, Wyllie and Field[12] have pointed out that regurgitation of gastric secretions into the lower portion of the esophagus can give rise to esophagitis and ulceration. Chronicity is, however, an important factor in the cases of regurgitation and ulceration, and that has not been present in the patients with acute bulbar poliomyelitis.

Conclusion

In view of the present information it would appear that in bulbar poliomyelitis gastrointestinal ulceration and/or perforation with or without hemorrhage has been more frequent than previously supposed. Routine guaiac tests should be performed on the stools of all patients with acute bulbar poliomyelitis in order to recognize the presence of gastrointestinal bleeding as early as possible. Preparations for blood transfusions should be included with the measures instituted by the alert physician who cares for these desperately ill patients since, as demonstrated by Case 1, this condition is not irreversible.

Summary

Five patients with severe bulbar poliomyelitis complicated by gastrointestinal perforation and/or hemorrhage are presented. A detailed case report is given in the one patient who recovered. The electrophrenic respirator was instrumental in maintaining this patient's respiration and massive blood transfusions in preventing shock from intestinal hemorrhage.

The gastrointestinal complications of bulbar poliomyelitis appear to be more frequent than previously realized. A relationship between midbrain damage and gastrointestinal lesions, as emphasized by Cushing, occurring during the course of acute bulbar poliomyelitis, is postulated.

Acknowledgment

The authors wish to make grateful acknowledgment to Dr. R. C. Eley and Dr. C. A. Janeway for helpful advice.

Addendum

Recently one of the authors (S. J. S.) has had occasion to participate in a review of a portion of the poliomyelitis postmortem material at the Children's Home Hospital in Utica, N.Y. Two cases were encountered which are of interest in regard to this publication.

The first was R. C., an 11 year old boy who died of bulbospinal poliomyelitis. At autopsy the stomach was found to be full of coffee-ground material. There were six small areas of definite ulceration as well as marked generalized congestion in the stomach.

The second patient, M. V. T., a 15 year old female, had vomited coffee-ground mucus several times prior to death. She had had bulbospinal poliomyelitis. At autopsy, the stomach was found to contain a large amount of coffee-ground material, and just above the cardia there was a perforation 1 cm. in diameter in the center of a hemorrhagic area. Another more linear perforation about 3 cm. in length was present in the mid-esophagus. The left pleura contained about 800 cc. of coffee-ground material.

Smith et al.[13] recently made mention of two patients who had perforated peptic ulcers. Operative repair was made on one of these who subsequently recovered. This again illustrates that although this type of lesion occurs in desperately ill patients, it is not necessarily fatal.

References

1. Bibliography of Infantile Paralysis 1789-1944 with Selected Abstracts and Annotations, edited by M. Fishbein, compiled by L. Hektoen and Ella M. Salmonsen, Philadelphia, J. B. Lippencott Company, 1946.
2. Erskine, F. A., Mason, J. H., and McDade, H., Perforation of esophageal ulcers in bulbar poliomyelitis, Am. J. Med. 8:239, 1950.

3. Heyde, E. C., and Robinson, S., Acute peptic ulceration accompanying bulbar poliomyelitis: Report of two cases, Gastroenterol. **11**:519, 1948.
4. Sarnoff, S. J., Maloney, J. V., Jr., Sarnoff, L. C., Ferris, B. G., and Whittenberger, J. L., Electrophrenic respiration in acute bulbar poliomyelitis: Its use in management of respiratory irregularities, J.A.M.A. **143**:1383, 1950.
5. Weinstein, L., Personal communication to the author.
6. Rundlett, E. V., Mauriello, D. A., and Thomas, J., Personal communication to the author.
7. Wilson, J. L., Personal communication to the author.
8. Cushing, H., Peptic ulcer and midbrain, Surg., Gynec. & Obst. **55**:1, 1932.
9. Sarnoff, S. J., Sarnoff, L. C., and Whittenberger, J. L., Electrophrenic respiration. VII. Motor point of phrenic nerve in relation to external stimulation, to be published.
10. Farber, S., Personal communication to the author.
11. Neuhauser, E. B. D., and Berenberg, W., Cardioesophageal relaxation (chalasia) as cause of vomiting in infants, PEDIATRICS **5**:414, 1950.
12. Wyllie, W. G., and Field, C. E., Etiology of intermittent oesophageal regurgitation and haematemesis in infants, Arch. Dis. Child. **21**:218, 1946.
13. Smith, E., Graubard, D. J., Falcone, J., Givan, T. B., and Feldman, A., Clinical management of acute poliomyelitis, J.A.M.A. **144**:213, 1950.

SPANISH ABSTRACT

Lesiones Gastrointestinales en la Poliomielitis Bulbar Aguda

Los autores reportan cinco casos de poliomielitis bulbar aguda complicada con hemorragia y perforación intestinal.

Se describe en detalle la historia clinica de un paciente que finalmente se recobró. Los movimientos respiratorios de éste paciente fueron mantenidos mediante el uso del respirador electrofrénico. Tranfusiones masivas de sangre fueron administradas para prevenir el shock consecuencia de hemorragias intestinales.

Los autores estiman que las complicaciones gastrointestinales de la poliomielitis bulbar aguda ocurren mas frecuentemente de lo sospechado previamente.

Se sugiere la posible relación entre las alteraciones del cerebro medio y las lesiones gastrointestinales ocurridas durante el curso de la poliomielitis bulbar aguda.

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ELECTROENCEPHALOGRAM AND EYE DISORDERS

Clinical Correlation

By JULIAN D. LEVINSON, M.D.,* ERNA L. GIBBS, MANUEL L. STILLERMAN, M.D., AND MEYER A. PERLSTEIN, M.D.
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THIS preliminary report concerns itself with the authors' observation that many children in whom the electroencephalogram showed occipital foci had abnormalities of the eyes. To elucidate further the nature of this relationship, a detailed study was made of 1281 children under 16 years of age. This study is limited to the relationship between the electroencephalographic findings of occipital foci and neuro-ocular pathology in general. A more detailed evaluation of this relationship relative to types of strabismus, fusion status, amblyopia ex anopsia, etc., will form the basis of a subsequent report.

DISTRIBUTION OF CASES

The case material was divided into two groups—one comprising 676 cases in whom complete history and neurologic and eye examinations were available. Of this group, 460

TABLE 1

EEG IN NORMAL AND CEREBRAL PALSIED CHILDREN IN RELATION TO PRESENCE OR ABSENCE OF EYE PATHOLOGY

Clinical Classification		Total Cases	EEG Classification in Per Cent				
			Normal	General Seizure Activity	Focal Abnormality		Total
					Occipital	Other	
Normal		180	98	0	0.5	1.5	100
"Normal" with Strabismus		36	70	0	30	0	100
Cerebral Palsy	Eyes Normal	305	26	1	38	35	100
	With Strabismus or Other Eye Disorders	155	17	0	74	9	100
Total		676					

were a consecutive series of cerebral palsy cases seen in a pediatric-neurologic office and clinic practice. The remainder of this group was made up of 180 normal children without neurologic or ocular pathology, and a group of 36 children with strabismus who were otherwise "normal." Table 1 shows this distribution, with reference to the presence or

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* Deceased.

absence of eye findings. No significant relationship to sex, race or age was noted, so that these subclassifications were omitted from the table for purposes of clarity.

The second group with which this study is concerned consisted of 605 children with abnormal EEGs in whom a record of the eye findings was available, but in whom complete histories and physical findings were not given (table 4).

Nature of Eye Disorders

In the total group of 1281 cases, eye disorders were noted in 397 instances. Strabismus was the most common condition noted and accounted for 73% of the total ocular pathology. Amaurosis was noted in approximately 16%. The remaining 11% consisted of paralysis of vertical gaze, congenital cataracts, nystagmus and congenital anomalies. Visual aura are not included as "eye findings" in this study, although high correlation with occipital foci was noted.

Technic

All EEGs were taken with the patient awake and asleep. Sleep was either natural or induced with ¾ to 1½ grains of seconal. Sleep records were considered necessary for the proper study of

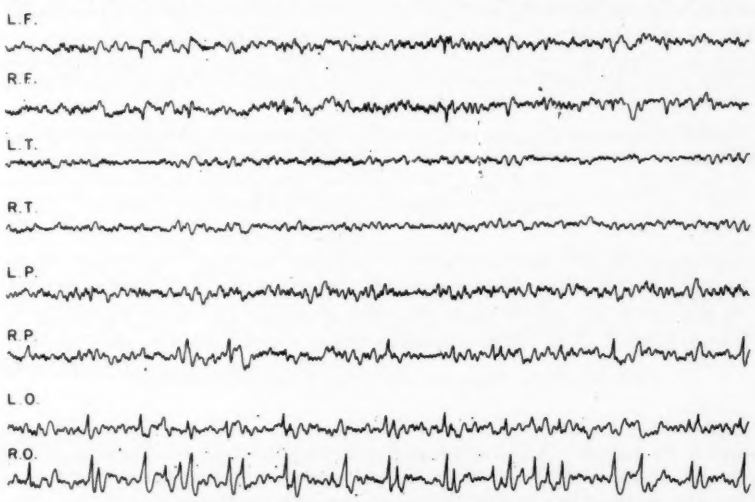

Fig. 1A. EEG showing large spikes, in occipital region, mainly on right.

this series, since during sleep a much greater proportion of abnormalities become manifest in the EEG.[3]

Pathology was considered to be present only when large spikes or a definite slow wave focus (S_2) occurred[2, 3] (Fig. 1A and B). For purposes of this study the electroencephalographic abnormalities were divided into the generalized group, in which the seizure activity occurred simultaneously in all leads, and the focal group, in which the electroencephalographic disturbance occurred independently in 1 or more areas.[4] The focal group was further subdivided into those with and those without occipital involvement. The former group included those in which the occipital area was involved alone or in combination with other areas.

Results

(See table 1.) In 180 control children, namely, those with no history of seizures and completely normal physical examinations, only 0.5% had occipital foci. In 36 children with strabismus but otherwise normal, 11 (30%) had abnormal patterns in the occipital leads. Of these 11, 4 had

spikes or slow wave foci. The remainder had marked and persistent amplitude asymmetry between the right and left occipital leads and limited to this area. The present experience indicates that such a high degree of asymmetry is an abnormal finding, since it did not occur in the normal control group.

The group of 460 cerebral palsy cases includes some patients with pyramidal tract and some with extrapyramidal tract involvement, some with and some without seizures, some with and some without eye findings. In this group (table 1) a high incidence of electroencephalographic abnormalities is present, but most of these, as would be expected, are of a focal nature. Of the 305 cases without neuro-ocular disorders, 38% had occipital foci, and 35% had abnormalities in other leads. In the 155 cases with eye involvement, the percentage with occipital involvement was twice as great as in the group without eye involvement.

To determine whether a correlation existed between the type of eye involvement and the presence

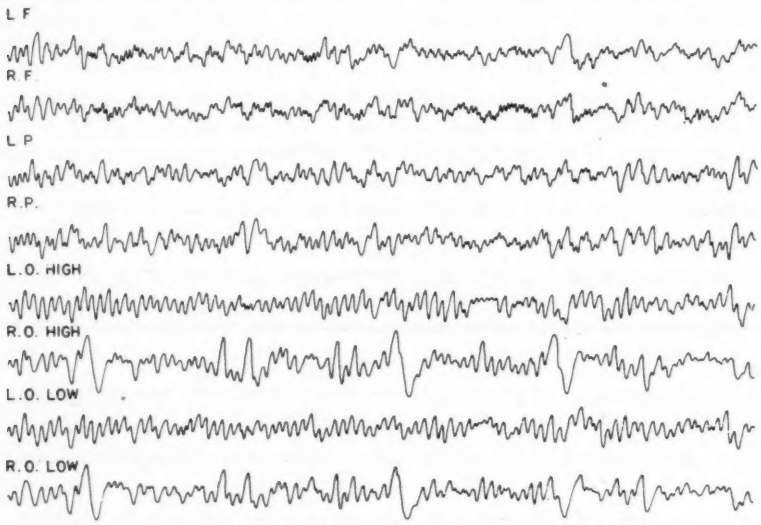

FIG. 1B. EEG showing slow wave focus in right occipital region.

of occipital foci, the 155 cerebral palsy cases with neuro-ocular pathology were tabulated according to the type of eye disorder. It can be seen from table 2 that of 105 cases with strabismus, 80 (76%) had occipital foci, and of the 24 cases with central blindness, 22 (92%) had occipital foci. In the other categories, too few cases were observed from which to draw conclusions.

Since, in cerebral palsy, there is a high correlation between the presence of clinical seizures and electroencephalographic abnormalities, it was thought advisable to see whether this correlation was affected by the presence or absence of eye pathology. Table 3 shows the relationship between the electroencephalographic findings in cerebral palsy and the presence or absence of clinical seizures and neuro-ocular aberrations. It is obvious that the presence of seizures in cerebral palsy increases the incidence of focal seizure activity throughout the brain,[5] including occipital involvement. Table 3 shows that even in the absence of neuro-ocular deviations, the incidence of focal occipital electroencephalographic abnormalities is doubled (52% to 25%) when seizures co-exist. However, when in addition to seizures eye disorders are present, a significantly greater percentage of focal electroencephalographic changes occur than when the eyes are normal (82% to 52%). The high incidence of occipital foci noted in table 2 must be interpreted as being due not only to the incidence of ocular abnormalities, but also to the fact that this population consists entirely of children with organic brain disease.

The second portion of the study consisted of 605 patients with a history of seizures and whose

TABLE 2

ELECTROENCEPHALOGRAPHIC FINDINGS IN VARIOUS TYPES OF EYE DISORDERS

155 Cerebral Palsy Cases

Eye Disorder	Total Cases	EEG Findings		
		Normal	Occipital Foci	Other Foci
Strabismus	105	14	80 (76%)	11
Blindness (Central)	24	1	22 (92%)	1
Paralysis of Vertical Gaze	14	6	8	
Nystagmus	6	6		
Congenital Cataracts	3		3	
Optic Atrophy	2		2	
Microphthalmia	1			1

EEGs demonstrated focal abnormalities. The correlation with the presence of eye disorders was noted (table 4).

Of 253 patients with abnormal electroencephalographic foci sparing the occipital region, only 9% had eye pathology. Of 352 patients with occipital foci, 52% had abnormal neuro-ocular findings. When one considers foci limited to a specific area of the brain, it can be seen from the table that occipital involvement is associated with clinical eye deviations over 8 times more frequently (63%) than when isolated involvement of frontal (3%), temporal (6%) and parietal (8%) areas occurs.

Strabismus comprised approximately 75% of the eye cases in this group, central blindness about 20% and nystagmus, cataracts, or a combination of the above, the remainder. In this group also, as in the first group studied, blindness and strabismus were the ocular deviates most frequently associated with abnormal occipital foci (92% and 76%, respectively). (See table 2.)

DISCUSSION

This preliminary study has indicated that, in a significant number of children with either strabismus or central blindness, there are demonstrable changes in the occipital leads of the EEG, primarily demonstrated on sleep records. This is present regardless of whether organic brain disease or seizures exist.

TABLE 3

RELATION OF EYE FINDINGS TO EEG

Correlation with Presence of Seizures in 460 Cerebral Palsy Cases

Clinical Classification		Total Cases	EEG Classification in Per Cent			
			Normal	General Seizure Activity	Focal Seizures	
					Occipital	Other
Eyes Normal	No Seizures	172	37	1	25	37
	With Seizures	133	13	2	52	33
With Eye Disorders	No Seizures	105	21	0	71	8
	With Seizures	50	6	0	82	12

While the results obtained in cases of cortical blindness were not wholly unexpected, the correlation in strabismus was striking. This may point the way to a new diagnostic tool for a better understanding of the etiologic factors in the vexing problem of strabismus, where the question often arises as to whether local pathology of the extraocular muscles, dysfunction of the peripheral nerve or its nucleus, or some central nervous system abnormality is responsible.[6]

Cases of paralytic strabismus, i.e., those due to involvement of cranial nerves III, IV and VI or their nuclei, or those due to disease or anatomic variation in the individual

TABLE 4

LOCALIZATION OF ELECTROENCEPHALOGRAPHIC FOCI AND EYE DISORDERS

605 Cases with History of Seizures

Location of Focus	Total Cases	No. of Cases with Eye Disorders	% of Cases with Focus Showing Eye Disorders
Frontal Only	34	1	3
Temporal Only	98	6	6
Parietal Only	51	4	8
Multiple—No Occipital	70	11	16
Total other foci without occipital	253	22	9
Multiple with Occipital	216	98	45
Occipital Only	136	86	63
Total occipital with or without other foci	352	184	52

muscles, do not usually present difficulty in diagnosis. However, the greater number of cases are nonparalytic (concomitant) in origin. It is in this group that further detailed study correlating electroencephalographic findings with ocular motility and with the sensory mechanisms may shed further light on supranuclear influences.

The role that electroencephalographic studies will play in the diagnosis of neuro-ocular disorders will be better clarified in these detailed studies which have been initiated. The EEG may become a useful diagnostic tool to be used in association with other methods of study to solve the riddle of the sensorial aspects of the squint problem. Too much emphasis has been placed on the motor aspects of ocular deviation by the average ophthalmologist, and insufficient attention has been drawn to the sensory components. It is possible that electroencephalography may be of value as a test for the integrity of the neuro-optic pathways and visual cortex, and that visual psychologic testing may do the same for the relatively unexplored associational pathways. It may be that the defective link in many strabismus cases lies in these associational pathways, and that visual agnosias, aphasias or defective fusion mechanisms and not a motor factor, is the dominant cause of the deviation.

It is probable that ocular pathology limited to the peripheral organ does not affect the electroencephalographic patterns of the brain. In three such cases which were observed, one retinoblastoma and two traumatic lesions, the EEG was normal.

Summary and Conclusion

A preliminary report is presented of electroencephalographic studies, both awake and asleep, on 1281 children under 16 years of age with respect to the presence of eye abnormalities, particularly strabismus.

Thirty per cent of 36 children with strabismus but otherwise normal, and only 0.5% of 180 children entirely normal, had occipital abnormalities on their EEGs.

In children with organic brain disease causing cerebral palsy, electroencephalographic foci in the occipital region occurred almost twice as frequently in the presence of abnormal eye findings. This relationship prevailed regardless of the presence or absence of seizures.

In patients with eye disorders, electroencephalographic foci involving the occipital region were six times more common than all other foci combined.

On the basis of this study, it would seem that children who show some neuro-ocular disorder should have a careful study of their EEGs for the detection of a possible central basis for their pathology. Conversely, patients who show an occipital focus on EEG should have a thorough ophthalmologic examination to rule out eye abnormalities.

References

1. Gibbs, E. L., and Gibbs, F. A., Diagnostic and localizing value of electroencephalographic studies in sleep, Proc. A. Research Nerv. & Ment. Dis. **26**:366, 1946.
2. Gibbs, F. A., and Gibbs, E. L., Atlas of Electroencephalography, Cambridge, Mass., Addison-Wesley Press, 1950.
3. Gibbs, F. A., Gibbs, E. L., and Lennox, W. G., Electroencephalographic classification of epileptic patients and control subjects, Arch. Neurol. & Psychiat. **50**:111, 1943.
4. Gibbs, E. L., Merritt, H. H., and Gibbs, F. A., Electroencephalographic foci associated with epilepsy, Arch. Neurol. & Psychiat. **49**:793, 1943.
5. Perlstein, M. A., Gibbs, E. L., and Gibbs, F. A., Electroencephalogram in cerebral palsy, Proc. A. Research Nerv. & Ment. Dis. **26**:377, 1946.
6. Riley, H. A., Central nervous system control of ocular movements and disturbances of this mechanism, Arch. Ophth. **4**:640 and 883, 1930.

Spanish Abstract

Electroencefalograma en los Trastornos Oculares

Los autores presentan un estudio electroencefalografico realizado en 1281 niños menores de 16 años durante el sueño y despiertos, con respecto a la presencia de trastornos oculares particularmente la ocurrencia de estrabismo.

Se encontró que un 30% de 36 niños normales a excepción del estrabismo y un 0.5% de 180 niños completamente normales, demostraron alteraciones del EEG.

En niños con paralisis cerebrales debido a lesiones organicas del cerebro las alteraciones electroencefalograficas de la región occipital fueron dos veces mas frecuentes cuando el estrabismo estuvo presente. Esta relación se mantuvo independientemente de la presencia o ausencia de convulsiones.

La ocurrencia de alteraciones electroencefalograficas focales de la region occipital en pacientes con trastornos oculares fué seis veces mas frecuente que en todos los otros focos combinados.

Basándose en éste estudio los autores recomiendan una investigación cuidadosa del EEG en niños que demuestren trastornos neuro-oculares, como un medio posible en descubrir una causa etiologica central. Igualmente, en pacientes que demuestren un foco occipital en el EEG deben estudiarse desde el punto de vista oftalmológico para así eliminar trastornos oculares.

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Pediatrics

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AMERICAN ACADEMY OF PEDIATRICS, INC. PROCEEDINGS AND REPORTS

THE PRESIDENT'S PAGE

OFTEN officers or members of the Board are asked questions concerning the Academy meetings. This letter is written to answer these questions.

The Academy now holds one areal meeting and one general meeting a year. For a time an attempt was made to have two areal meetings a year. Since it is difficult to interest commercial firms in that many meetings, it resulted in a deficit, which the Board felt we could not afford. Occasionally now the areal meetings do lose money, but the Board has felt that one such meeting is indispensable. The annual meeting results in a profit. The areal meeting this year is in Cincinnati; the annual meeting will be in Toronto. Next year the areal meeting will be in Washington, and the annual meeting in Chicago.

The Board has debated whether to hold most, if not all, the general meetings in Chicago. There are three advantages in this: it is centrally located, facilities are available, and the central office is located there. They would like your opinion as to the wisdom of doing this.

Each year the areal meeting is held in a different part of the country and its program is arranged completely by the men in the locality in which it is held. It has speakers, symposia, and panels; and most often they are outstanding. Sometimes comparisons are made between the excellence of the areal meeting and the annual meeting. They are not really comparable, for their composition is significantly different.

When it was first held, the composition of the annual general meeting was like the areal meeting, except that the annual business meeting was held at this session. During the years, the annual meeting has grown in scope. The first change was the addition of the round table. At first only a few were offered and, when their popularity was assured, more and more have been added. At the last annual meeting there were 47 round tables. They are groups of 35 members with a discussion leader, and their value has been their informality. Now and again a number of leaders have been in charge and have spoken, and in reality they resembled a panel. The Board has discouraged this and limits now the number of leaders to one or two, putting the emphasis on the discussion.

Probably these round tables attract more members than any other one feature of the annual program.

The Borden and Mead Johnson Awards are also a feature of the annual meeting.

Another recent addition is the holding of two day seminars before the opening of the general session. For these two days a member can take a concentrated course on any subject that is offered. Ten seminars were held at the last meeting.

This last year educational films for professional and lay groups were shown continuously throughout the meeting. The value and popularity of this were demonstrated by the fact that there were over 1700 in attendance.

In Chicago there was another innovation which was successful enough to be repeated this coming year. Two semipopular evening meetings were held to which wives were invited. Also for the first time, evening meetings of the sections were held. These occurred just before the opening of the main meeting.

This year still another feature will be added. Each of the sections will hold a meeting the day before the regular session. These will be held during the daytime and will be devoted to the field in which the section is interested and will be technical in nature, the discussion being aimed at the members of the section. The surgeons will discuss surgical technic, the allergists technic in allergy, and the Section on Mental Growth and Development will discuss those technics in which they are interested. While these meetings are arranged for the section members, any member of the Academy may attend any of them that he desires and, indeed, is urged to do so.

This coming year, a greater correlation will be attempted between the discussions in the meetings themselves and the scientific exhibits which will be shown.

It will be seen from this that the Academy made a definite attempt over the years to stress the importance of the programs in the education of its membership. It is a much larger task than is generally realized to arrange the annual program. It has to be fairly well in hand six months before it is held, and completely so three months before it takes place. Members often write in a few months or even weeks before this meeting, wishing to sponsor a certain paper or contribution. It is impossible to make late changes of any magnitude. The Program Chairman of the Academy is in charge of this meeting. He literally begins his plans one year in advance, and it is a continuous job for the whole year.

Nothing has been said of the fun and fellowship at these meetings which year after year is more evident. Believe me, that is important.

PAUL W. BEAVEN, M.D., *President*

Pediatrics

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SPECIAL SECTIONS

THE PEDIATRICIAN AND THE PUBLIC

AN OPEN FORUM

PAUL A. HARPER, M.D., *Editor*

Statements appearing in this column do not necessarily reflect the opinion of the editor nor are they to be interpreted as the official opinion of the Academy.

THE first communication is a statement by the American Board of Pediatrics on the importance of better training in the care of the well child during its period of growth and development.

The second communication is by Dr. Frederick D. Mott, Acting Deputy Minister of the Department of Public Health in the Province of Saskatchewan. Dr. Mott is an authority on medical care in rural areas and is senior author of *Rural Health and Medical Care* (McGraw-Hill, 1948), an outstanding source of information on health conditions and medical services in the rural areas of the United States. This communication requires reference to an earlier statement in the *Journal of Pediatrics* (**31**:228, August, 1947) by the Canadian Medical Association in which that association approved the principle of health insurance and maintained the opinion that health insurance programs should be developed by the various provinces in accordance with their local needs. Dr. Mott's paper describes what has been done in Saskatchewan.

A STATEMENT BY THE AMERICAN BOARD OF PEDIATRICS ON TRAINING REQUIREMENTS IN GROWTH AND DEVELOPMENT

The recent study of child health services in the United States by the American Academy of Pediatrics revealed that a pediatrician on an average day spends 54% of his time in health supervision of well children. This trend is destined to increase, because the people of the United States for a variety of reasons are increasingly demanding health supervision for infants and children. Governmental agencies, not the least of which now are the Armed Services, are vitally interested in the extension of health supervision to the entire infant and child population.

The American Board of Pediatrics has a serious responsibility which it has adequately assumed in assuring all people that pediatricians are qualitatively adequately trained for

the health supervision of our young population. Indeed, some years ago, foreseeing this need, it incorporated into its examinations a section on growth and development which is weighted at least 25% of the examination. There can be little doubt that evaluation of candidates for proficiency in health supervision of infants and children is best ascertainable by assessing the adequacy of their information in the field of growth and development.

It is outstanding, however, to observe that candidates continue to present themselves for examination by the Board disproportionately unprepared in the field of growth and development. It becomes difficult therefore to draw any conclusion other than the fact that pediatric training centers have not been dynamic in adapting to a changing situation by incorporating such training into their programs adequately. Although the Board has never assumed the function of specifically outlining training programs, it would be derelict in its responsibility if it did not call attention to certain over-all deficiencies in pediatric training.

The Board does not believe that pediatricians should be less adequately trained in the care of the sick infant and child. It does believe, however, that a study of growth and developmental processes can be advantageously incorporated into such training. One of the outstanding defects of current candidates is the fact that on the basis of examination requirements they have didactically mastered a certain number of facts relating to growth and development without understanding the practical implications of these facts. They thereby indicate that this information is not incorporated into their daily practices. This also is a reflection of the fact that when teaching in growth and development has been presented, it has often been didactic in character with a view toward fulfilling Board requirements rather than by a meaningful incorporation of this material into daily pediatric practice.

It becomes obvious, therefore, that pediatric training centers must increasingly assume the responsibility for the day-to-day teaching of growth and development in a clinical setting. This means a practical evaluation of the total development of each patient and its meaning to parents and physicians. It also means that some opportunity to observe presumably well infants and children become part of the training program where it is not at present. Intensive study of relatively few patients longitudinally provides an opportunity to teach not only growth and development but the importance of continuity of pediatric care which is an important element of pediatric practice. Indeed, it may be questioned whether pediatric training centers which do not provide such opportunities should be accredited for two years' training in the same sense that the Board recognizes the limitations of training in a contagious disease hospital by offering training credit for only a maximum of six months.

The concept of growth and development should remain a broad one. In some centers there has been a tendency to regard this sphere of teaching as including only physical growth; in other centers the emphasis has been predominantly on emotional growth. We are interested primarily in providing the prospective pediatrician with the tools for the most optimal practice. This means the teaching of physical, mental, emotional and social growth and their interrelationship since one of the most important functions of the pediatrician is the guidance of the total growth, development, and ultimately social adjustment of the individual. Since the teaching needs of individual residents is so dependent upon personal background, the individualization of teaching and the necessity for a preceptorship-like arrangement is evident. The resident must have an opportunity to have his work and study observed individually.

In this light, it would obviously be unwise for the Board to prescribe any stereotyped teaching program. That each training center can work out an adequate, individual program adapted to its own situation and personnel has been amply demonstrated. Even the compilation of bibliographies is probably undesirable although these were believed necessary by the Board in the past. Any such compilation often becomes a maximum rather than a minimum study program. And adequate references and bibliographic compilations have become abundantly available in recent years.

It is to be emphasized that the Board recognizes that only pediatricians themselves adequately trained in growth and development can teach effectively. While other personnel (nutritionists, anthropologists, psychologists, psychiatrists) may participate advantageously at various times, only the pediatrician is in a position to teach by example. At the resident level this is probably the most effective teaching technic.

This statement is presented, not with the idea of making something different of pediatricians or pediatric education. Rather it is intended to strengthen both, and to render both more adequate for their responsibility of caring for the total health of children.

UNIVERSAL COVERAGE HEALTH INSURANCE IN SASKATCHEWAN

By FREDERICK D. MOTT, M.D.*

It is apparently not yet a matter of general knowledge throughout the United States, or even throughout Canada, that two of Canada's 10 provinces have embarked on programs of universal coverage health insurance. Both in Saskatchewan and in British Columbia programs of compulsory hospital care insurance are in operation, Saskatchewan's program having started on January 1, 1947, and British Columbia's on January 1, 1949. In Saskatchewan, moreover, there has been in operation since July 1946 an experimental or pilot plan in compulsory medical care insurance in a large area comprising the southwest corner of the province, which borders on Montana and Alberta.

It would seem to be desirable that there be much wider knowledge of these significant programs, particularly among the professional groups on both sides of the border who have a very direct and vital interest in developments of this kind. The purpose of this article will be to give a rather general account of the two Saskatchewan programs, avoiding minor details and extended statistical analyses of services and costs. While a discussion of the British Columbia Hospital Insurance Service is beyond the scope of this paper, it may be noted that the pattern of hospital care insurance adopted by British Columbia is very similar to that established two years earlier in Saskatchewan.

Situated just north of Montana and North Dakota, Saskatchewan is an extension of the Great Plains region. The intensely rural character of the province and its agricultural economy must be borne in mind as one weighs the experience of the medical and hospital care insurance programs under review. The whole province is almost as large as Texas, but most of the people live in the southern half of the province, in an area as large as New York, New Jersey, and all the New England states combined. This southern part of Saskatchewan, which has a population density of less than seven persons per square mile, is for the most part wheat-growing and ranching country, with approxi-

* Chairman, Health Services Planning Commission, and Acting Deputy Minister, Department of Public Health, Government of Saskatchewan.

mately 80% of the population living on farms and in small communities of less than 2,500. There are only four centres in the province with more than 10,000 people; the largest city has a population of about 70,000.

In this rural situation, in which all the problems of rural medicine are typically represented, the people have acquired over the years a highly-developed health consciousness. Through cooperative and governmental action going back more than 35 years, they have learned how to tackle some of their more acute health problems and to find practical, working solutions. Saskatchewan has, in fact, won an enviable reputation throughout Canada for pioneering in the development of basic health services. This pioneering tradition is very much alive today.

Perhaps best known of all the health developments in Saskatchewan are the municipal doctor plans which had their origin many years ago. As early as 1914, local units of government known as rural municipalities were offering retainers to attract physicians to their communities. Within a few years, salaries were offered and the system of municipal doctor plans emerged, a pattern studied and recommended for rural areas by the Committee on the Costs of Medical Care.[1] The municipality embarking on such a program taxes itself typically through a property levy, sometimes through a personal tax, and offers a salary and free office space to the doctor. At the present time there are 112 rural municipalities—more than one in every three—with medical care plans in operation, not all on a salary basis, but some on a fee-for-service basis. Similar plans are in operation in over 40 towns and villages, covering virtually all residents of these communities.

Certain other health programs deserve at least brief mention in order to round out the background of current developments in the general field of health services in the province. An outstanding program of tuberculosis control has been built up over the years, with such concrete evidence of its success today as that the death-rate for whites was down to 13.1 per 100,000 in 1949 and the fact that there are more than five sanatorium beds per annual death from tuberculosis at the present time. For many years there has been no charge to the patient for the care of tuberculosis in Saskatchewan.

The cancer control work in the province is another notable program, which had its origin 20 years ago. There are modern cancer clinics in Regina and Saskatoon, to which patients may be referred by any physician in the province. Diagnostic work at these clinics has been freely available for years and for the past six years, not only the diagnosis but also the treatment of cancer has been completely on a tax-supported basis. Every cancer patient is entitled to receive without charge all services required, including diagnostic procedures, radiologic therapy, surgical care, and hospitalization.

Mental services have also been on a tax-supported basis for years, with no means test and no charge to the patient.

As in the case of the cancer control and mental services programs, there has been a general acceleration in the process of extending health services in Saskatchewan in the past six years. Dr. Henry Sigerist of Johns Hopkins was called in by the present government after their election in 1944 to make a survey and submit recommendations. The outlines of the present health program are to a considerable extent the out-growth of the work of the Health Services Survey Commission headed by Dr. Sigerist.[2]

Quite rightly the development of full-time public health services has been given a high priority in recent years. Local units of public health administration, which, apart from two separately administered city health departments, are called "health regions" in

Saskatchewan, have been planned to cover the populated southern half of the province. The concept is that the unit, based on a natural geographic area, will be a unit for all health services, not just for public health but for medical care purposes, too. Logical major trading areas are defined, surrounding major trading centres and composed of four or five subsidiary trading districts within the region. Of 14 proposed regions, six have been established with public health programs, with another about to go into operation, and one of the existing regions has undertaken the program of medical care insurance to be described later in this article.

Along with the development of full-time public health services, attention was given after the Sigerist survey to meeting the medical care needs of the public assistance recipients including old age and blind pensioners, mothers who receive special allowances for dependent children, and similar related categories. Since January 1, 1945, this entire group has been entitled to receive on a tax-supported basis the services of physicians, hospitalization, essential drugs, fairly complete dental care, and certain other types of benefits including eye-glasses, appliances, physiotherapy and special nursing. This program is administered by the provincial Department of Public Health with the assistance of a committee of physicians nominated by the Saskatchewan Division of the Canadian Medical Association.[3]

Bearing more directly on the provincial hospitalization program to be described, there has been an active hospital construction grant-in-aid program in effect since 1945, supplemented since 1948 by federal hospital construction grants. Largely as a result of this program, in which 95 hospitals have received aid to date, hospital facilities in Saskatchewan have increased to a ratio of 6.5 beds per thousand by rated capacity and 7.8 beds per thousand actually set up. These figures, which are as high as any found in Canada, exclude federal hospitals, sanatoria, and institutions for mental patients and for custodial care.

The Saskatchewan Hospital Services Plan

Organized health services having been made available to deal with special conditions such as tuberculosis, cancer and mental illness, and to deal with the general needs of the public assistance groups in the population, it was natural that Saskatchewan would turn to the task of establishing a comprehensive program of health services to meet all the needs of the entire population. At this point an important decision was made, that province-wide health services would be introduced by stages and that the first program undertaken would be one of compulsory hospital care insurance. Accordingly, the Saskatchewan Hospitalization Act was enacted by the Legislative Assembly in 1946 and the far-reaching program for which it provided went into effect on January 1, 1947.

Administrative responsibility for the operation of the Saskatchewan Hospital Services Plan was originally assigned to the Saskatchewan Health Services Planning Commission but transferred to the Department of Public Health in 1950 when the functions of these two health agencies were combined in one department. As is customary in the Canadian form of government, the Department is under a responsible Minister of Public Health, an elected Member of the Legislative Assembly who is also a member of the Executive Council. In the administration of the Hospital Services Plan, the Department makes full use of special advisory committees and regular meetings are held with the Executive of the Saskatchewan Hospital Association.

The Plan covers all residents of the province except those already provided for by

federal or provincial programs for special groups or special conditions and includes 92% of the population. Indigents are included among the beneficiaries through payment of their tax by that agency of government, municipal or provincial, responsible for their care. Participation is compulsory except for a few thousand trappers and fishermen in the Far North who may join on a voluntary basis.

The Hospital Services Plan is financed by a personal tax or premium supplemented by funds from the general revenues of the province. The annual personal tax rates are $10 for each person over the age of 18 and $5 for each dependent under 18, with a family maximum of $30. The tax is collected through almost 1,000 municipal offices throughout the province, a commission being paid for the service. There are arrangements for payment of the tax on an instalment basis, but the majority of taxpayers pay the entire annual tax in a lump sum, in advance.

In 1950 the proceeds of the personal tax are meeting about 50% of the total cost of the hospital care program. The balance is made up from general provincial revenue. This is in accord with sound social insurance financing which, in the absence of a tax graduated to incomes, must recognize a reasonable limit on individual contributions.

The benefits provided through this program are practically complete. Based on public ward or minimal accommodation, they include virtually all the special services provided by a particular hospital. The extra cost of private or semiprivate accommodation is paid by the patient. Among the benefits are the use of the operating room, surgical dressings and casts, x-ray and other diagnostic procedures including laboratory tests of all kinds, x-ray therapy, anaesthetic drugs and equipment, physiotherapy, most drugs in general use, and blood plasma. Within the province, no limit is imposed on the length of stay in hospital for which the Plan will make payment, provided that inpatient care is medically necessary. The only important limitation on the service is the exclusion of outpatient benefits. Moreover, there are no restrictions because of age or pre-existing conditions, no dollar limits for diagnostic services or drugs, and no waiting periods for maternity or other benefits. Provision for hospital care outside Saskatchewan is on an indemnity basis, with the period of care restricted, with certain exceptions, to 60 days.

As was to be expected, coverage of the entire population including the aged, the chronically ill, and the indigent, the lack of limitation on days of care or other restrictions, and the high ratio of beds available, have resulted in high utilization rates.[4] The large volume of hospital care being received by the people of Saskatchewan through this program considerably exceeds the amount typically provided through voluntary Blue Cross plans. The incidence of hospitalization in 1949 was 200 cases per 1,000 covered population, or one person in five, as compared to 178 cases per 1,000 in 1948 and 156 cases in 1947.[5]

The incidence of hospital care varies considerably with age. It was highest in 1949 among children of less than one year and second highest among beneficiaries 70 or more years of age. Increases in the volume of hospital care from 1947 to 1949 have been most marked in these two age groups. Among children under one year of age (excluding newborn infants*), the incidence of hospital care increased from 195 cases per 1,000 in 1947 to 325 cases in 1949, or by more than 66%. Among beneficiaries 70 or more years of age, the case rate increased from 255 per 1,000 in 1947 to 321 per 1,000 in 1949, or by 26%.

* In 1949 91.6% of all births occurred in hospital.

For all beneficiaries hospitalized, the average length of stay in 1949 was 10.3 days, as compared to 10.5 days in 1948 and 10.0 days in 1947. During the past three years, the average stay in hospital has decreased among younger age groups and increased among beneficiaries over 65. Among persons 70 years and over, the average length of stay in hospital increased from 20 days in 1947 to 21.5 days in 1949.

Total expenditures of the Hospital Services Plan in 1949 were $10,410,444 as compared to $9,204,893 in 1948 and $7,560,763 in 1947. The cost per head of covered population was $13.58 in 1949, $11.85 in 1948, and $9.68 in 1947. Half the increase in the total expenditures has been due to an increase in the number of days of care for which the Plan has made payment and half has been due to higher rates of payment to hospitals, reflecting their higher operating costs.

Administrative costs have been remarkably low, illustrating that government operation of a program of this kind can be highly efficient. The first year, administrative costs amounted to 8.1% of total expenditure. These costs dropped to 6.5% in 1948 and to 5% in 1949. The figure will be well under 5% for 1950. One may compare such figures with the Blue Cross average of from 8 to 9%.

Under the Saskatchewan Hospitalization Act the hospitals throughout the province are being operated under independent management as always. The government has made it clear that it has no intention of taking over the hospitals and the general philosophy is that government control is unnecessary as long as hospitals will voluntarily maintain high standards and operate efficiently. At the same time, the provincial Department of Public Health tries to assist the hospitals in every way to raise the standards of care. On the staff of the Department are technical experts in hospital administration and in radiologic, laboratory, nursing, pharmaceutic and dietary services whose function is to provide the hospitals with expert consultative services. Moreover, training courses and institutes for hospital personnel are being conducted or sponsored by the Department in cooperation with hospital authorities and bursaries from both provincial and federal funds have been established for training in hospital administration, in nursing instruction and supervision, and in various technical fields. Special grants have also been available to aid hospitals in the improvement of their diagnostic facilities. In these various respects, the program of the Department of Public Health in relation to hospitals and hospital care goes far beyond that attempted by any voluntary hospital care insurance plan. To an increasing extent, the program related to hospital standards is a cooperative one in which the organizations representing the hospitals and hospital personnel are working closely with the Hospital Services Plan and the Division of Hospital Administration and Standards of the Department.

A final point about the Hospital Services Plan that deserves mention, and that is closely related to the maintenance of high standards of hospital care, is that a method of paying hospitals for their services has been worked out in consultation with the hospitals themselves which virtually assures them sufficient revenue to cover their total operating costs, provided that they are managed efficiently and maintain a satisfactory but not excessive occupancy. One might make bold to say that serious operating deficits are a thing of the past in Saskatchewan. Stable financing, incidentally, has a very definite bearing on sound hospital planning. Through the hospitalization program there can be assurance of maintenance of rural hospitals located in areas which under ordinary circumstances would find it impossible to support such facilities.

What we have here, then, is the application on a broader basis of the time-tested principles learned through the Blue Cross movement—prepayment of the costs of care, a service contract rather than an indemnity contract, and free choice of hospital for the patient. To these familiar principles have been added those of universal coverage, unrestricted benefits, governmental support, and the right of indigents to full participation in the program. Another distinguishing feature of the new program is that there is not only governmental financial participation, but there is active support to hospitals as they strive to improve standards of care.

A Pilot Plan of Compulsory Medical Care Insurance

Looking forward to the day when the second major step toward a comprehensive health service for the entire province may be taken, the Provincial Government sponsored appropriate legislation and fostered the establishment on July 1, 1946, of an experimental or pilot plan of universal coverage medical care insurance. This program, which has now completed 4½ years of successful operation, was developed in the Swift Current Health Region, a 12,000 square mile area in the southwest corner of the province. It covers every person and family residing in this area except those already entitled to services through some special federal or provincial program. It is important to stress at the outset that the initiative came from the people in the area, who voted by a considerable majority to adopt the program. Thus they exercised their democratic right of going to the polls and voluntarily electing to adopt a compulsory program.

The medical care program in the Swift Current Health Region is administered by a democratically elected Regional Health Board of 12 members. How this Board is constituted may be of interest. The Region includes 31 rural municipalities and some unorganized territory as well as 36 villages, six towns, and the City of Swift Current. The total population is slightly over 50,000. In each of four public health districts within the Region, there is a district health council composed of members appointed by each of the rural and urban municipalities within the district. These health councils in turn, and the Swift Current City Council, elect representatives to the 12-man Regional Health Board.

The role of the Regional Health Board in respect to the public health program is an advisory one, but in dealing with medical services, the Board is the executive body.[6] The Board employs a secretary-treasurer and clerical staff to administer the medical care program and the Regional Health Officer, who is an employee of the provincial Department of Public Health, participates in all meetings of the Board as an advisor. The coordination of public health and medical care activities within the Region is facilitated by housing both administrative staffs side by side in the Regional Health Centre in Swift Current.

The medical profession in the area has had a close and cooperative working relationship to this program from the beginning. A medical advisory committee representing the district medical society meets with the Regional Board from time to time and all contractual arrangements are arrived at by mutual agreement. Moreover, the assessment of physicians' bills is handled by a retired doctor in consultation with two other private practitioners, all being appointed by the medical society. Special referrals of patients outside the Region are handled in a similar manner.

While the Regional Health Board must submit its proposed budget each year to the

Minister of Public Health for approval, and while regulations adopted by the Board must likewise meet with the approval of the Minister, the Board comes very close to being an independent body, having wide latitude in developing its program of medical and related services for residents of the area.

It is worth repeating that the population coverage in this pilot plan is very broad. Generally speaking, everyone who has lived in the Health Region for three months is eligible for benefits and liable to pay the required tax. Those for whose care the Federal Government is responsible, such as Indians and members of the Armed Forces, are excluded. The same applies to the group of public assistance recipients for whose care the Provincial Government is responsible, including old-age and blind pensioners and recipients of the mothers' allowance. Altogether, there are over 48,000 people participating in the regional program out of a total population of about 50,000.

The services provided through the Swift Current program, while not comprehensive, are broad by ordinary standards and go far toward meeting the needs of the people in the area. They include medical, surgical, and obstetric care rendered by physicians within the Region, referrals to specialists outside the Region on a somewhat limited basis, a full-time radiologic service, hospital outpatient services, and limited dental care for children up to 16 years of age. Inpatient hospital care is provided, of course, through the province-wide Hospital Services Plan.

The basic service in this regional program is the care provided in the office, home, and hospital by the 35 physicians practicing in the Region. The patient is entirely free to choose any physician he wishes and to change doctors when he so desires. The physicians are in ordinary private practice as before, with their own offices or group practice clinics. The services include all essential services which the physicians in the Region are capable of rendering—preventive, diagnostic, medical, surgical, and obstetric services. There is no direct charge to the patient for any of these services except for a mileage charge for home visits.

Referral services outside the Region have presented certain difficulties. Originally, any patient could be referred to a specialist or any other physician outside the Region by his family physician and 75% of a standard fee would be paid. The volume and cost of referral services began to get out of hand, however, and in 1950 the Regional Health Board and the district medical society decided to reduce these services, which they thought were being abused. Referrals are now confined to conditions requiring special skills not found within the Region or they must be authorized by a special committee of physicians. Moreover, payment is now made at 50% of the fee schedule, with the patient responsible for paying the balance.

A notable feature of the Swift Current program has been the employment by the Regional Health Board of a full-time radiologist who is at the service of the physicians and their patients throughout the entire Region. While he handles primarily the x-ray work at the Swift Current Union Hospital, the principal hospital in the Region, he makes periodic visits to main district hospitals to handle the more difficult radiologic procedures. Moreover, films are sent to him to interpret by general practitioners from outlying points in the Region. A somewhat similar arrangement is now being worked out covering a tissue pathology service, but in this instance, the pathologist will serve at least one adjacent health region as well as the Swift Current Region.

Another major benefit is the provision of outpatient services by the 12 hospitals in

the Region. Outpatient facilities in the usual sense are rather limited in the predominantly rural hospitals concerned, but those services that are available are all benefits under the program. They include such diagnostic measures as laboratory tests, basal metabolism tests, electrocardiograms and x-rays. Also made available are certain treatment services, including physiotherapy and the use of the operating or emergency room for accident cases or conditions not demanding actual admission to a hospital bed. In having these outpatient services available to them, the people in the Swift Current Region are enjoying a benefit which many throughout the province would like to see added to the Hospital Services Plan as a province-wide benefit.

Finally, the Regional Health Board has attempted the difficult task of providing dental care for children up to 16 years of age. Largely because of the acute shortage of dentists in rural districts in Saskatchewan, the Board has employed four dentists plus auxiliary personnel on a full-time basis and they would like to augment this staff if personnel could be obtained. The services are rendered largely through the use of mobile units, but permanent dental clinics are also being established. A fixed clinic is already found in the Regional Health Centre and others are planned for three district health centres. The program is not simply one of examinations and prophylaxis; it includes fillings and any other services the salaried dentists can provide. A limited emergency service is also maintained, with payment being made to private dentists when no clinic is within reach.

This broad program of medical, dental and outpatient care is financed almost entirely by the Health Region itself. Of the annual budget of approximately $700,000, the people within the Region contribute about 90%, with provincial grants accounting for the remaining 10%. The Region's large share of the total revenue required is raised mostly through a compulsory personal tax or premium, with about one-fourth coming from the proceeds of a 2.2 mill property levy on every property owner in the area. In 1950 the personal tax was $15 for a single person, $24 for a family of two, $30 for three and $35 for a family of four or more. The provincial grants are made to help finance special services. Thus the Provincial Government makes annual grants covering 50% of the cost of dental, radiologic and outpatient services, up to a certain maximum in each case. A substantial annual grant is also made to facilitate the assembling of statistical information. It should be noted that these various figures have no reference to the cost of the public health program, which is borne one-third by the Health Region and two-thirds by the Provincial Government.

The entire procedure of collecting both the personal and property taxes is relatively simple. Collection of each tax is handled by the various rural and urban municipalities, which receive from the Region a commission for this service. The property tax is simply added to the annual levy otherwise payable by the property owner. The personal tax is payable annually in advance at the town hall or the rural municipal office. The collection of both of these taxes throughout the Region has been remarkably good, considering that the entire Swift Current area is a rather notoriously drought-stricken and poor crop area.

It is notable that indigent persons or families for whom the municipalities are responsible have their tax paid on their behalf by the municipalities in which they reside, and they receive the same kind of health service card and the same benefits as do self-supporting residents of the Region.

Observations and Evaluation

Here, then, in one of Canada's Prairie Provinces we find universal coverage programs of medical and hospital care insurance in operation and in a sense taken for granted by the people concerned. Some of what has been accomplished so far could be called experimental, but its character is rapidly changing to that of proved demonstration. These programs deserve study, for they are undoubtedly the forerunners of programs with similar objectives that will be developed in the coming years in Canada and the United States. A detailed evaluation of these programs will not be attempted in this article, but certain general observations will be made which are felt to be quite valid.

In the first place, one may ask what participation in either of these programs has meant to the people for whom they were established. It is clear that in making essential care available on the basis of need and in affording security against the costs of unpredictable illness, they have meant a great deal. Each program is popular—one might almost say that each program is strikingly popular. Criticisms are heard, of course, coming from scattered individuals and occasionally from some interested organization. Any criticism, however, is usually directed at some gap in either program, illustrating the marked desire of people in the province for the establishment of a comprehensive program that will cover the entire range of health services. It has seemed quite remarkable that residents of the Swift Current Health Region have had little complaint to offer even though out-of-region benefits have had to be curtailed. By popular request the Region has been enlarged to take in people in adjacent areas who have been anxious to share in the benefits of the medical care program. In certain of the other Health Regions in the province, moreover, there is a considerable demand for starting similar medical service plans, although none has actually been established as yet. Similarly, there has been a wide-spread demand for the same kind of dental care plan for children as that operated in the Swift Current Region, and plans of this kind have in fact been initiated in most of the other regions.

The province-wide hospitalization program is almost universally popular. Political parties other than the party in power at this time have been quick to recognize this and their pronouncements are characterized by assurances that they favor the continuation of the program in essentially its present form.

While cautious at first in their references to the Hospital Services Plan, practising physicians have come to appreciate fully the benefits of this program to themselves as well as to their patients. They are not only in a position to hospitalize those patients who require such care and to order such special services in hospital as they feel may be desirable, without worrying about the financial circumstances of the patients, but they are also in the pleasant situation of having a better chance to collect their own accounts because their patients are not burdened with hospital bills. The physicians complain occasionally about the pressure which certain patients place on them to be admitted to hospital, and they point out that this pressure would be less if there were provision for payment for diagnostic services in outpatient departments and in physicians' offices, but at the same time practically every physician in the province will readily testify that the program is basically sound and that it represents a worth while social advance.

Turning to the Swift Current medical care program, which affects the physicians concerned far more directly, one may ask what the program has meant to the doctors practising in the Region. In a report published in 1950 one of the senior physicians in this area has told why he and his colleagues wish the program to continue.[7] In this

report he acknowledges that the program involves "a certain amount of over-work" and that there is always "some misuse of such a system by both patients and doctors." He also points out that a certain amount of difficulty has been encountered in reaching agreement with the Regional Health Board about the size of the annual fund budgeted to pay doctors' bills. He emphasizes in his report, however, that the program has meant greater security and stability for both doctor and patient. The following quotations from this report are revealing: "I do not think there is any doubt but that doctors in the Swift Current Region have better incomes under this system. . . . I feel certain that a return to private practice would reduce the number of doctors in the area . . . personally I cannot see how a voluntary system would work in this area."

A brief note about physicians' incomes in the Swift Current Region may be of interest. In 1949, with payment on a limited fee-for-service basis from a fund of $423,000, the active practitioners in the Region earned an average gross income of about $14,000, not counting income from other sources. The figure for 1950 is not yet available, but it will be higher, since the fund for 1950 was increased to $445,000. The fact is that such an income picture is quite remarkable in a very sparsely settled, chronically poor crop area such as southwestern Saskatchewan.

If hospital administrators and trustees are genuinely concerned, as many of them are, about the impact of compulsory hospital care insurance, they should by all means visit Saskatchewan and talk with their counterparts in large and small hospitals throughout the province. They would doubtless hear a few complaints, but by and large they would find that the Hospital Services Plan is not only accepted but that hospital people generally would not think of going back to the old days before the province-wide program was established.[8] The chief reason for this is that the Hospital Services Plan has stabilized hospital financing, even though the four years of its existence have coincided with a severe inflationary period. The financial base has been provided for rising standards of service and this has been accomplished at a time when all over Canada and the United States the increasing range of services provided by hospitals and the rapidly increasing price level have acted together to make the provision of modern hospital care, at a cost which patients can pay, a matter of constant worry for hospital administrators and boards.

It is commonly argued that health insurance programs covering entire population groups should not be undertaken until the medical and hospital resources are available to meet the demands that will be placed upon them. It has been maintained by others, on the contrary, that the best and perhaps the only way to bring medical and hospital resources up to the level of adequacy is to establish broadly based prepayment programs which mobilize and spread medical purchasing power. A very strong argument to back this latter position is found in the Saskatchewan experience. In the Swift Current Region, for example, the number of physicians has increased since the program began four years ago from 19 to 35, an increase definitely greater than in other parts of rural Saskatchewan. Similarly, the existence of the hospital care insurance program has meant that hospitals could be built where needed, even in remote districts, because their maintenance was assured through payment for all beneficiaries from the provincial fund. It is quite evident, in fact, that this program has given a very strong emphasis to hospital construction and it is perhaps the most significant factor in Saskatchewan's leadership in Canada today in the number of general hospital beds for its population.

While the existence of any broadly based prepayment program does not in itself

guarantee that services of higher quality will be available, it can be stated from the experience in Saskatchewan that the health insurance programs have had a definite tendency to improve the quality of medical and hospital care. The physicians in the Swift Current area have not only been providing a larger volume of care to residents of the Region, but they are furnishing much more in the way of diagnostic services. With adequate and stable incomes, they have been able to add to the diagnostic facilities available in their offices and clinics, and with no economic barrier between the patient and his physician, they have been able to use these facilities as required. So far as the quality of hospital services throughout the province is concerned, I believe that observers would agree that our hospitals as a group are in better shape today than ever before, with much new equipment, improved diagnostic and therapeutic facilities, and general maintenance right up to par. In short, a higher quality of hospital care is being made available to the entire population, a situation which would hardly prevail if the individual were still responsible for his hospital bill or if only one or more limited voluntary hospital care insurance plans were in operation.

Another observation is that not only has compulsory health insurance been shown to work in Saskatchewan, but the programs are notable for their combining of the essential principle of clearcut responsibility to the public which is served with the equally important principle of constant regard to the interests of the participating professional groups. It is vitally important that organized professional groups be brought into a close advisory relationship to responsible administrative agencies, and this has been done. Where strictly professional matters are involved, the profession should be brought into the administrative framework itself, and this, too, has been done in the Swift Current pilot plan.* That adherence to these principles is conducive to harmonious working relationships is seen in the fact that the physicians in the Swift Current Health Region are on the best of terms with their Regional Health Board, which is essentially a governmental body.[9] There is also the best of feeling between the Hospital Association and the provincial Department of Public Health.

A further significant point deserves mention. Administration of the Saskatchewan Hospital Services Plan by the Department of Public Health, in association with a broad range of public health and medical care services of other kinds, has shown the advantages of unified and coordinated administration of a health program by the official health agency of the province.

While these programs of universal coverage health insurance are operating quite smoothly in Saskatchewan today, a number of problems are naturally being encountered or are inherent in the situation and should be recognized. Many problems of varying degrees of importance have been solved, of course, as the programs have evolved, but certain basic questions remain to which answers must be found.

One problem that at the moment defies solution in a Canadian province, but which would not necessarily be so serious in one of the States, is that of financing. Under a postwar agreement between most of the provinces and the Federal Government, a province cannot impose a tax that is graduated according to income. Accordingly, both the personal hospitalization tax and the principal tax employed in the Swift Current Health Region are flat taxes for an individual or for a family of a certain size that bear no relation to the

* This has also been done in the medical care program for public assistance recipients, where the "Central Medical Assessment Board' is nominated by the medical association.

income of the particular person or family. A family of four in the Swift Current Region must pay a combined tax or premium of $65 a year for medical and hospital care, regardless of income level, and it may pay a property tax as well. It is obvious that this type of taxation is questionable from the standpoint of equity and, in actual practice, quite a number of medically indigent families find it difficult to pay the regional tax or, in fact, to pay the hospitalization tax in other areas in the province.

Aside from the essential inequity of taxation not graduated to income, there is also the related problem of how to assure stable financing of programs of this kind in a province with an agricultural economy that is subject to marked fluctuations depending on climatic conditions and the price trends in world markets.

The fact is that the Swift Current Health Region is probably too limited a base to assure stable financing of the medical care program over the years. More substantial subsidies from the Provincial Government would help, but here again, to anyone familiar with Saskatchewan's history during the drought-stricken thirties, it is clear that the province itself, with its limited sources of revenue, faces special problems in attempting to finance an undertaking as large as a comprehensive health insurance program. In short, it is essential that there be federal participation in the financing of far-reaching social programs of this kind. It is worth noting that every major political party in Canada is on record as favoring the development of a nation-wide system of health insurance and its implementation appears to await only the stabilizing of the international situation and reduction in expenditures for national defence. How long a postponement this means for the further development of health insurance in Canada, no one can predict today.

Another major problem, and one of wide interest, is that of devising suitable controls to ensure the wise and discriminating use of medical and hospital services that are made available with little or no economic barrier between the patient and his physician or hospital. It is a problem which deserves far more intensive study than it has received so far. It has many aspects, involving as it does "human nature" as displayed by the patient and those who serve him, administrative regulations, methods of payment for services, the availability of suitable alternative services or facilities, and other factors that will occur to the reader. In Saskatchewan, the problem of controls is faced chiefly in connection with the hospitalization program and here one finds that the answer is complex, involving among other things greater awareness of basic social responsibilities by the general public, physicians, and hospital administrators and boards of trustees, the development of a system of paying hospitals that will not constitute a financial inducement to over-utilization of hospital facilities, the provision of diagnostic services in outpatient departments and in physicians' offices and group clinics, the development of suitable alternative facilities for selected elderly and chronically ill patients, and the organization of home care services. Progress is being made in dealing with several of these factors and much is being learned along the way.[10]

The administrator of medical or hospital care insurance cannot but be impressed with the central position of responsibility of the individual practising physician in respect to this whole question. It is the physician who largely determines the number of office, home, or hospital visits that a given patient will receive, who writes out and hands the patient a prescription for drugs, who admits a patient to hospital, and who decides when the patient can be discharged from hospital. When physicians individually and in their organizations come to face squarely the new responsibilities placed on them through

the operation of prepayment plans—and there are hopeful signs of this development—the problems of suitable controls in medical and hospital care programs will dwindle in significance.

A third major problem, and a highly important one, relates to the quality of medical services. It is all too easy for those concerned to become preoccupied with solving the problem of how to pay for medical care, perhaps neglecting to concentrate sufficiently on the vital question of the type of care the individual patient receives when he needs it. Fortunately, the whole matter is being studied by a number of individuals and interested groups.[11] In addition to the references made previously to certain efforts to raise the quality of services in Saskatchewan, it might be mentioned here that the question involves, of course, a very wide range of subjects for exploration, such as the need for more and better trained medical and hospital personnel of all kinds, the need for regular refresher courses and a variety of opportunities for postgraduate training, the desirability of introducing team-work into medical practice through the organization of group practice clinics, and the need to expand and extend today's experiments and demonstrations in developing the concept of regionalization.

Closely related to the problem of quality of services is that of ensuring that in the development of health insurance programs there will be emphasis on the prevention of disease and on building positive health. There is the danger that over-burdened physicians may become preoccupied with treatment services, largely to the exclusion of orderly and unhurried personal preventive services. Health insurance can and must be much more than a new method of payment for medical care. There must be a determined and sustained effort to see that the emphasis in any over-all medical care program is placed on the prevention of illness and on building positive physical and mental health.

If this objective is to be attained, if we are to harness the powerful forces which will be set into play with removal of the economic barrier between patient and physician, it would seem that certain distinct but inter-related courses of action are indicated. It is clear, for example, that ways must be found to spare the physician for essential tasks which he alone is fitted to perform and to help him carry out his work efficiently. He must have readily at hand adequate hospital accommodation for his patients, adequate diagnostic facilities, and access to full consultative and referral services. Through the provision of needed facilities, through the assigning of certain tasks to others, and through improvements in methods of organization of health services, much can be done to create the conditions under which physicians can function most effectively.

One measure which universally deserves a high priority is the extension of full time public health services. The official local health agency, administered under the direction of a trained health officer, will play a key role in the coordination of community and personal health services. It is vitally important that a close partnership be built up between the practising physician and the health department. The private practitioner must be brought closer to preventive medicine in its many phases and, on the other hand, the health officer and his staff can supplement the efforts of the family doctor and ease the burden under which he works.

A well organized community public health agency can help the physician by assessing the socio-economic factors involved in certain illnesses, by giving assurance that family and other contacts are being followed up, by providing consultant services such as those available through mental health clinics, by educating the general public in the proper

use of health services, by providing laboratory services, by analyzing morbidity and mortality statistics to point up major health problems in the community, and by carrying out those large-scale preventive tasks where a mass approach is clearly indicated.

While the importance of protecting the physician under health insurance and supplementing his services has been stressed, the basic point must be recognized that a comprehensive program of health insurance provides the practitioner an opportunity to practise medicine that is positive in its nature and preventive in its approach. Not only is the economic barrier between the patient and himself removed, but the physician has at his command all of those diagnostic and other tools essential to good practice. While health insurance will mean for the medical profession pressures beyond those encountered in ordinary practice, at the same time it offers every practitioner a challenge to see that medical science plays its full part in the attainment of the objective for all people of a state of physical, mental, and social well-being.

References

1. Committee on the Costs of Medical Care, Medical Care for American People, Chicago, University of Chicago Press, 1933, pp. 90-91 and 121-122.
2. Sigerist, H. E., Report of Saskatchewan Health Services Survey Commission, Regina, Thomas H. McConica, King's Printer, 1944.
3. Annual Report of the Health Services Planning Commission for Calendar Year, 1948, Regina, Thomas H. McConica, King's Printer, 1950.
4. Taylor, M. G., Utilization and costs under compulsory prepaid coverage, Canad. Hosp. **27**:31, 1950.
5. Annual Report of the Saskatchewan Hospital Services Plan, 1949.
6. Mott, F. D., Pattern of local services in Saskatchewan health program, Am. J. Pub. Health. **39**:216, 1949.
7. Matheson, J. A., Report to Central Health Services Committee, College of Physicians and Surgeons of Saskatchewan, on Swift Current Health Services, Saskatchewan M. Quart. **14**:359, 1950.
8. Report of Saskatchewan Hospital Association, Thirty-second Annual Convention, Oct. 11 and 12, 1950.
9. Kelly, A. D., Swift Current experiment, Canad. M. A. J. **58**:506, 1948.
10. Taylor, M. G., Saskatchewan Hospital Services Plan, Thesis, Berkeley, Calif., University of California, 1949.
11. Quality of medical care in national health program, Statement by the Subcommittee on Medical Care, Am. J. Pub. Health. **39**:898, 1949.

TRENDS

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This and subsequent descriptions of events and trends are intended to be unbiased and factual, presenting both sides of controversial matters so that conclusions may be formed from critical appraisal of things as they are. These statements do not necessarily reflect the opinion of the writer nor are they to be interpreted as official opinion of the Academy.

FAMILIAR HEALTH BILLS APPEAR IN THE 82nd CONGRESS

THE manifold problems related to the Nation's medical manpower overshadow other aspects of health legislation in the early days of 82nd Congress. These problems are dealt with so fully in the daily press, in weekly releases from the American Medical Association and local medical societies, that there is little to be gained in commenting upon them here; the story would be old before it appeared in print. There are, however, other measures to which we wish to call attention. Certain major health bills which were given active consideration in the 81st Congress have reappeared—as we predicted they would—in the 82nd Congress. These are, in chronologic order of their introduction:

NATIONAL HEALTH INSURANCE

A bill (H.R. 27) to provide a national health insurance and public health program was introduced on January 3 by Representative Celler of New York. This is the Administration's version of compulsory national health insurance, identical with H.R. 345 introduced into the last Congress by the same author.

Support for this measure appeared in President Truman's budget message to Congress when he again renewed his recommendations for the establishment of a medical care insurance program. He said: "Such a program would require a 2-year starting period before health benefits become available. During that time, a small payroll tax of one-half of 1 percent would be levied to accumulate a starting reserve, estimated at $275 million for 1952, and covered into a trust fund to defray initial administrative and developmental expenses. These expenses, which would be made directly from the trust fund, are estimated at $35 million for 1952."

This recommended appropriation, as in the case of other proposed appropriations for bills not yet enacted, will not be made unless the related bill is passed by Congress.

Senator Murray, Chairman of the Senate Labor and Public Welfare Committee, is said to have indicated that nothing will be done with the National Public Health Insurance Bill until after the Committee has received the report of a special committee set up to study health services and health insurance. This latter committee is under the Chairmanship of Dr. Dean Clark, formerly Medical Director of the Health Insurance Plan of Greater New York, and now Director of the Massachusetts General Hospital. The report originally was due on February 1, but it is now called for by March 31.

SCHOOL HEALTH SERVICES

Also on January 3, Representative Coudert of New York introduced a bill (H.R. 42) to provide for school health services. This bill is identical with its counterpart, H.R. 4352,

introduced into the 81st Congress by the same author. It may be noted that the new version still contains the clause which has been cited as objectionable by the American Medical Association, i.e., permitting treatment of physical and mental defects regardless of economic status of parents.

Federal Aid to Medical Education

A bill (S. 337) to provide an emergency five year program of grants and scholarships for education in the fields of medicine, osteopathy, dentistry, public health, and the nursing profession was introduced January 11 by Senator Murray. This bill is sponsored by all the Democratic members of the Senate Labor and Public Welfare Committee to which the bill has been referred. Emphasis now is placed upon the immediate need to meet the prospective requirements of the armed services. A companion bill, H.R. 1781, identical to S. 337 has been introduced into the House by Representative Klein of New York.

The President gave special attention to this matter in his budget message. He said: "Our chronic shortage of doctors, dentists, and nurses will be aggravated as more of them are called into the Armed Forces. Therefore, we need, more than ever, prompt enactment of legislation that will help to increase enrollment in medical and related schools, by assisting them to meet their costs of instruction and to construct additional facilities where needed. Scholarships should be provided to attract larger enrollments in nursing schools, and grants should be made to states for vocational training of practical nurses."

The President included in his budget a tentative appropriation of $30 million to implement proposed legislation to authorize:

1. Premium payments to medical, dental, degree nursing, and public health schools for each student enrolled in excess of its average past enrollment and smaller payments per student based on average past enrollment.
2. Grants to medical, dental, degree nursing, and public health schools for construction of additional facilities.
3. Grants to states for practical nurse training.
4. Scholarship aid to students in fields in which there is a shortage of qualified applicants, particularly nursing.

In comparison to S. 1453 in the 81st Congress, this new bill contains several increases in the proposed allocations. Federal assistance could reach 50% of the total cost of instruction; the old bill provided 40%. Whereas the former bill provided $5 million for purposes of construction and equipment, the sum of $25 million is now proposed. In other respects the new bill is essentially the same as the old bill with provision for allowances to schools for additional new students, scholarship stipends and amounts for other health personnel.

It may be recalled that in the 81st Congress the bill for federal aid to medical education was passed by the Senate but was not reported out by the House Interstate and Foreign Commerce Committee. The Senate Labor and Public Welfare Committee has already opened the discussion on S. 337 but as of present date (Jan. 29) has taken no action.

Also according to present information,* there is another bill due momentarily for federal support of medical schools. A bill, which is expected to be introduced by Repre-

* Washington Report on the Medical Sciences No. 190, Jan. 29, 1951.

sentative Burnside, has for some weeks been in the process of preparation with the help of several medical school deans. The Burnside Bill, as currently drafted, proposes a five year $300 million program of expansion of medical and dental schools. One half the sum would be used for outright grants to construct and equip new medical schools; the remainder would be for enlargement and improvement of existing schools in the health professions, including but not limited to medicine and dentistry. Teaching hospitals also would be eligible beneficiaries, provided there was no conflict with provisions of the Hill-Burton Act.

Local Public Health Units

As previously noted in this column, the bill to provide for development and maintenance of local public health units was passed by the Senate in the 81st Congress, was reported favorably by the House Interstate and Foreign Commerce Committee but did not get by the House Rules Committee. This same bill now appears again as S. 445 introduced on January 11 by Senator Hill. In commenting upon this matter in his budget message, the President said: "The civil defense program will confront many communities with important public health responsibilities. Moreover, shifts in population arising from stepped-up defense production and increased mobilization will place heavier burdens on many communities to provide adequate sanitation, protect food and water supplies, furnish preschool and school child health services, and otherwise to prevent disease and promote the health of its citizens. Yet, a sizeable number of them lack the services of an adequately staffed local health department—even for their normal needs."

Research in Child Health and Development

Another familiar bill carried over from the last Congress is S. 676 introduced by Senator Douglas to promote federal support of research in child health and development. The bill provides for appropriations of $7.5 million for grants-in-aid and fellowships. A similar bill (H.R. 1879) has been introduced in the House by Representative Richard Bolling.

PUBLIC HEALTH, NURSING AND MEDICAL SOCIAL WORK

MYRON E. WEGMAN, M.D., *Contributing Editor*

PEDIATRICS, SOCIAL WORK AND PSYCHIATRY; OVERLAPPING DISCIPLINES

THE physician's special knowledge becomes of value to the patient only as it is applied through the "physician-patient relationship." Similarly, medical social workers have specific information about the social implications of disease processes. To be useful to clients this information must be applied through an inter-personal "worker-client relationship." Both relationships involve a rapport between individuals based on an awareness of what the content of the interview means subjectively, as well as objectively, to the client or patient. The inter-personal relationship, it seems to me, is of the essence in all professional work. It involves the lawyer, minister and architect. At its best, it is based on a sound, studied knowledge of personality structure. Here and there throughout the land pioneering efforts are being made to include, as an integral part of professional training, courses whose purpose it is to teach beginning professional students about the structure of the personality and simultaneously, as part of this process, give them insight into their own personality traits. It is inevitable that through this increased insight the students themselves are helped to mature. In numerous medical schools psychiatry is being included in the freshman year's curriculum in an effort to accomplish the same function. I believe that a course dealing with "Growth and Change" would serve medical students even more adequately than an early introduction to psychiatry, helpful as that may be, because the individual's growth and change involves too many values which are not primarily psychiatric, and psychiatry too many concepts not relevant to an orientation course.

Against this background, with its emphasis on relationship between people, I should like to consider the pediatrician's role in the care of children and parents, and to do this with the medical social worker's role in mind.

Pediatrics today is concerned not just with illnesses of children but even more their health and its preservation; not just with bodies, or minds or the two combined, but just as truly with feelings and intra-familial relationships and ultimate social adequacy. The discerning pediatrician is by this definition vitally concerned with parent-child relationships. It follows that he needs insight into the family background of his patients. In private practice he remains among the practitioners who go into homes and have more or less intimate personal insight into the way of life of their families. In the large portion of his work within hospitals and in clinics in which he lacks this contact he should have the collaboration of trained medical social workers. Every children's hospital owes it to its patients to have a department of social service integrated into its working structure to help the medical staff gain needed vital information about the child's situation in his environment and, if need be, to consider changes in that environment.

In considering family environment the basic relationship is that existing between parents and children. It is the foundation upon which the child's security as a person rests.

Adapted from presentation at National Conference of Social Work, 1949, American Association of Medical Social Workers.

It is predicated upon three ever-present factors; the personalities of the parents, the character of the child, and the environment in which the relationship develops.

I believe that parents can be superficially classified as to aptitude for caring for their children as follows: A large group, to whom parental function comes naturally for any of a number of reasons, such as membership in a large family, warmth of personality, or a high degree of emotional maturity, need relatively little instruction. Another large group with less natural aptitude nevertheless finds that it can use written or oral information easily. It does not take these parents long to feel at home in their parental role. The third group is smaller and includes parents who, because of their own emotional constitutions, are blocked from applying sound knowledge. In this group are found mothers and fathers with neuroses of varying kinds and degrees.

It has been helpful to me to have this crude categoric scheme in mind in selecting my approach to patients. It has kept me from belittling a woman from group I, who already has a fine sense of proportion about children, by offering her information which she already has; it has encouraged me to be at pains to apply educational technics to those in group II; and it has made me realistic in my dealings with the emotionally limited people in group III, for example, by not asking from them what they could not give.

At this point I should like to consider what can be done by the pediatrician for those in groups I and II—first for the children and then for the parents.

A few years ago the term "anticipatory guidance" came into prominence. For pediatricians the term means sharing of knowledge as to what is to be expected. Applied to the child, this includes such minor procedures as preparing him for an inoculation a moment before he receives it, by telling him that he is about to be given "a little pinch" on the arm—or if he is older, a needle or "shot"—that it will hurt a little for a very little while and that he will probably find that it is not painful enough to cry about, but that it is all right for him to cry if he needs to. The term also covers approaches to more complicated situations, such as having to go to a hospital or having to undergo an operation. In the former situation the child who has been told honestly and in some detail about how he will be living for the next few days has at least been given some real concepts to cling to, and been spared the need to conjure out of his imagination a conglomeration of fear-laden ideas. I know from personal observations that the reasonably stable child over 3 years of age who has had outlined for him in simple terms each step of what he is about to experience accepts what happens with assurance rather than panic. After the operation he adjusts realistically to postoperative discomforts and is quite free of panic states such as night-terrors which the child not so prepared often suffers.

Let us take, for example, preparation of a child for tonsillectomy. In a few minutes, I can tell him in terms of a story what he may expect to experience. I do this preferably a day or two before the operation, selecting this time because I believe that a longer interval would only give him more time to mull things over. After I have checked his physical condition, I tell him that he will be going to the hospital, up in an elevator to the laboratory, have his finger stuck so that a drop of blood may be drawn for examination, and then go up in another elevator to his room where he will be in a bed with sides and wheels on it. His mother will or will not be with him there, nurses will come in and out. Very likely while he is in his room, a nurse will bring him long white cloth boots and a white cap, and help him put these on. Finally, it will be time to go; he will be wheeled out in his bed, through the hall and onto an elevator which will take him down and then stop; its door will open and he, in his bed, will pass through the door into a

hallway. There he will see grown people dressed in white masks, caps, and gowns; some may stop to talk with him. After a bit, he will be wheeled into a room, helped from his bed onto a table and asked to lie on his back. A nurse or doctor will pour some medicine onto a cloth near his nose. The smell won't be too bad and all he needs to do is just what the anesthetist tells him to—blow the medicine away. Either before or after the anesthetist brings the cloth near his face, his eyes will be covered to protect them from the medicine. The medicine will make him sleepy and soon he will indeed be asleep. While he is sleeping, the doctor will be "fixing his throat." You will note that by not mentioning "cutting," "taking out," etc., which the patient does not actually experience, I have avoided an unnecessary reference to mutilating procedures. The story goes on thus. When he awakens he will be back in his room; his mother or a nurse will be there with him. He will feel bad, especially his throat where the doctor has been working. But everything is all done, and he will gradually feel better and better. It is all right to cry if he has to, but the quieter he is, the better he will feel. He will spend that night in the hospital and will be able to sleep a good deal. The next day he will go home and that night he will sleep just as always in his own bed. A few more days and he will be perfectly all right again.

Lest it seem inappropriate to have described the above procedure at such length, I hasten to point out that content of the discussion and attitude of the discussor are the essential factors. I believe that medical social worker who has the child's confidence can prepare him in his way just as well as the physician. A social worker in her contact with nurses and interns can easily teach such a technic. It is helpful if the parents are present when the child is being told about what is to happen. By being present they become sharers with the child in that part of the experience—a comfort both to the child and to them; their story will be consistent with reality and they may themselves see the whole procedure in a cooler light. Though it may seem a subtle point, the child's awareness that his own parents are there with him accepting the explanation lends legitimacy and acceptability not only to the story, but to the actual events which are to follow.

Similar forethought and purposeful sharing of information can help prevent chronicity and assure a return to health. The discharge of a patient when well should be as distinct a step in management of an illness as is recognition of the illness and beginning of treatment. It is not always easy to give up the secondary gains that sickness has brought and we can see this even in children. It happens much too often that a child goes home with explicit orders about medication to take and activities to avoid during convalescence, but no advice as to when these "standing orders" may be modified or dropped. As a result, parents continue to conceive of their child as abnormal and create an atmosphere consistent with illness rather than good health. Such an atmosphere makes it difficult for the child to consider himself truly well again, and thus makes for hypochondriasis.

Anticipatory guidance can be of great help to the well-balanced parent, both through delineation of normal baby and child behavior, and through interpreting it in terms of maturation. Thus the mother who knows that it is normal for her baby to hiccough; to sneeze to clear its nose; to cough to clear its throat; and to breathe irregularly is spared doubts as to the normality and wellness of her child. It is part of the role, not only of the physician, but also of the social worker to prevent anxiety from lack of information.

As the child grows older the same approach serves very well. Just as the parent may be taught to understand the meaning of sneezing and coughing, that parent may learn to understand that the acquisition of sphincter control is the taking over by the child of a

complicated function at a time when he is ready to assume its control. It is not "training" in the sense that teaching a dog tricks is "training." Efforts of the parent who understands this will be considerate not only of the child's physical mastery of the nerves and muscles which control the processes, but of the child's attitude. The objective is to have the child accept responsibility for his own functions. In so doing he is taking a step toward maturity and autonomy.

Transferring of responsibility for his own functions to the child when he is ready for such control is fundamental to good parent-child relationship and may help to reduce the need for rebellion often seen in adolescents who have been held too tightly in leash by their elders.

By respecting the integrity of our children, being considerate, kind and fair, and I should add, honest with them, we do much more than "prevent behavior problems." We create positive values in the children. Our idiom of interpersonal relationship becomes their idiom, and they incorporate into their personalities whatever of graciousness they sense in us. I am convinced that this transmission of positive values is as real and even more important than the transmission of negative values, which because it is painful, we single out for special attention in our recognition that the child's behavior disturbance is in large measure the result of mistaken handling by his parents.

So much for the reasonably well-adjusted parents of groups I and II.

When we deal with the emotionally unstable parents of group III, we quickly sense or painfully learn that a simple common-sense approach is not enough. We cannot just tell such people what to do. Social workers are keenly aware of the need to take emotional limitation into consideration. This is evidenced by a basic axiom in casework: "meet the client where he is." "Meeting the client" means recognizing him for what he is and accepting him for what he is, rather than a mandate to make him over through psychotherapy. Psychotherapy concerns itself with intra-personal or intra-psychic dynamics, the specific realm of psychiatry. Social work focuses its attention on inter-personal relationships. Its skills are in dealing with the individual's current situation with respect to people, economics and, among other things, groups. In this sense social workers and pediatricians, with perhaps a few rare exceptions, are not psychotherapists. Emotionally maladjusted people, however, are part of our case loads and practices. While both social workers and pediatricians recognize and accept emotional limitations and refer these people to others for psychotherapy, adjustment to the emotional limitations, through skillful use of the role of doctor to the child and utilization of the skill of the social worker as a teammate, can be most helpful. Surely, a time is coming when not only the doctor working in a hospital or public health setting, but also the physician in private practice will have available to him and find himself utilizing medical social workers as a matter of course.

The social worker can round out the physician's conception of his patient in terms of his day-to-day living; his relationships to his family, to other children, to his teachers at school; in fact, to all people or groups or institutions which impinge upon his life. Since these relationships are just as vital a factor in the child's well-being as vitamins or operations, the pediatrician should seek out and learn to utilize information from the medical social worker and discover the ways in which she can integrate her efforts with his.

Children, well and sick, are first of all people, and physicians and social workers, in proper teamwork with parent and child, can help them to be healthy people, in every sense.

EUGENE B. SCHUSTER, M.D.
Pittsburgh

NEWS AND ANNOUNCEMENTS

Continuation Course on Diseases of the Blood in Infancy and Childhood

Drs. William Dameshek, Professor of Clinical Medicine, Tufts University School of Medicine, Boston, Clement A. Finch, Associate Professor of Medicine, University of Washington School of Medicine, Seattle, and Robert W. Heinle, Associate Professor of Medicine, Western Reserve University School of Medicine, Cleveland, will participate in a continuation course on Diseases of the Blood in Infancy and Childhood to be presented at the Center for Continuation Study, Minneapolis, April 16-18, 1951. The course is given under the direction of Drs. Irvine McQuarrie and Charles D. May, Department of Pediatrics, University of Minnesota, Minneapolis.

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A Fellowship in Pediatric Neurology is available in the Children's Division of the Cook County Hospital. For information concerning this appointment, write to Dr. Abraham Levinson, Chief of Staff, Cook County Children's Hospital, Chicago 12.

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Pediatric Post-Graduate Course, Harvard Medical School, at the Burnham Memorial Hospital for Children, Massachusetts General Hospital, Boston, under the direction of Dr. Allan M. Butler, Professor of Pediatrics, June 11 through June 23 daily, 9 a.m. to 4:30 p.m. A broad review of pediatrics emphasizing the newer advances in diagnosis and therapy. For further information, write Courses For Graduates, Harvard Medical School, 25 Shattuck Street, Boston.

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The American Board of Pediatrics announces the following dates for oral examinations: Cincinnati, March 30, 31 and April 1, 1951; Atlantic City, May 5, 6, and 7, 1951.

ERRATUM

The Pediatrician and the Public, communication from Mr. I. S. Falk, vol. 6, November issue, p. 779, para. 5, line 2 should read: "of 16.4 patients of all ages, of which children accounted for 4.8 per day or 29 per cent. . . ."

BOOK REVIEWS

PARENT-TEACHER SERIES, Ruth Cunningham, Editor, New York City, Bureau of Publications, Teachers College, Columbia University, 60¢ each.

Understanding Young Children	Dorothy W. Baruch
Reading is Fun	Roma Gans
Answering Children's Questions	C. W. Hunnicutt
Being a Good Parent	James L. Hymes, Jr.
Discipline	James L. Hymes, Jr.
Your Child's Leisure Time	Mildred Celia Letton
Getting Along in the Family	Jane Mayer
Understanding Children's Behavior	Fritz Redl
A Good School Day	Viola Theman

The Bureau of Publications of Teachers College, Columbia University, is sponsoring a series of pamphlets intended for parents and teachers. At the present time the series includes the titles and authors given above. The topics chosen for discussion deal with situations and problems which are met daily by those who work and live with children. These unusual pamphlets were written by authors who are well versed in both the theoretic and practical aspects of child care and training. In simple language and winning terms they present to parents and teachers sound counsel and advice. Each pamphlet includes a number of neatly phrased generalizations which are aptly illustrated by numerous anecdotes and short case materials.

Pediatricians may care to refer parents to many of these pamphlets. Parents will find these pamphlets helpful on 2 scores: first, for the information which is presented, and, secondly, for the general philosophy of child care which is aimed at increasing the parent's self confidence. The relationships which exist between adults and children are viewed in the main with great kindliness and gentle humor. The materials offered are enlivened to a high degree by witty and clever pen drawings. The busy pediatrician should find these pamphlets a great aid to increasing parents' understanding and sensitivity to child behavior and experience.

In Memoriam

Leonard Gregory Parsons

LEONARD GREGORY PARSONS, B.S., M.D., F.R.C.P., F.R.S., an honorary member of the American Pediatric Society elected in 1935 and honorary fellow of the American Academy of Pediatrics since 1940, died suddenly at his home in Four Oaks, England, on December 17, 1950. He was 71 years of age. At the time of his death he was Dean of the Faculty of Medicine and Emeritus Professor of Paediatrics in the University of Birmingham, Consulting Physician to the United Birmingham Hospitals, and a member of the General Medical Council of Great Britain.

Born in Four Oaks on November 25, 1879, Dr. Parsons received his early education at Birmingham University and took his M.D. degree in the University of London in 1907. After a short period of practice and teaching, he volunteered for military service in 1914, was commissioned Captain in the R.A.M.C., and later promoted to Major when he was put in charge of the medical service in one of the military hospitals at Salonika. He was decorated with the Order of St. Sava by the Serbian Government.

Although his practice was not confined to children, the problems of pediatrics dominated his interest and in the main directed the lines of his scientific inquiry. As Physician to the Children's Hospital of Birmingham, he organized an active research laboratory and provided the inspiration for a highly productive group of investigators, whose contributions attracted world-wide attention. Under his leadership the Birmingham school soon forged to the front among the pediatric centers of Britain. Dr. Parsons published a number of important papers on celiac disease and other disorders of nutrition, on pink disease, on congenital malformations, and on various forms of anemia. In 1933, together with Mr. Seymour Barling, he edited a two volume text, *Diseases of Infancy and Childhood*. He was in the forefront among students of hemolytic disease of the newborn infant (erythroblastosis fetalis) and in recent years was engaged in defining the role of liver function in the pathogenesis of kernicterus. Always in great demand as a speaker among his own countrymen, he was invited in 1931 to give the Rachford Memorial Lectures at the University of Cincinnati, and in 1946 he was Blackader Lecturer before the Canadian Medical Association. Among other honors accorded him in the course of a distinguished career may be mentioned vice-presidency of the Second International Congress of Pediatrics, presidency of the Section on Disease in Childhood of the Royal Society of Medicine, presidency of the British Paediatric Association, and the award of the Moxon Medal of the Royal College of Physicians. During World War II he was indefatigable in organizing the emergency medical service throughout the Midlands, and in recognition of his contribution to the welfare of his country he was knighted in 1946. Two years later he was elected a Fellow of the Royal Society, an honor shared by only one other clinical pediatrician, the late Sir Thomas Barlow. It would be difficult to know which of these two—knighthood or fellowship in the Royal Society—pleased him the more.

A man of great modesty, unlimited kindness and genuine friendliness, Dr. Parsons exerted leadership through his gift of conveying enthusiasm for an all-out effort, in which every participant has the opportunity to play his part. His high regard for sincerity and for effort evoked the best that anyone was capable of contributing and bound his

colleagues to him with loyal devotion. There was no trace in him of authoritarianism or snobbishness; indeed, his singular facility in putting people at their ease and in lowering the barriers of natural reticence made him the most companionable of learned men. His fondness for children revealed itself in his peculiar skill in talking with them as equals and in evoking a spontaneous sharing of their interests.

He is survived by Lady Parsons, a son, Dr. Clifford G. Parsons, a daughter and three grandchildren.

Among pediatricians of this country and Canada are many who counted Dr. Parsons their friend and who readily sought his advice and counsel. In his death pediatrics has lost a wise and devoted leader, the influence of whose life and work will be felt for time uncounted.